

**ASSESSING HEALTH BELIEFS OF WOMEN DIAGNOSED AND AT-RISK FOR
FABRY DISEASE**

by

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ABSTRACT

Previous published literature examining the impact of Fabry disease on female heterozygotes has suggested that women with this disease have a unique clinical relationship with the healthcare system and engage in Fabry disease medical management in a manner different from their male counterparts. The past history of labeling these women as carriers for the disease and asymptomatic has been proposed as one barrier to females' participation in evaluation and monitoring for Fabry disease. However, the health beliefs unique to females with Fabry disease have not been thoroughly addressed in the literature. We attempted to examine this issue in more detail utilizing the Health Belief Model, a conceptual framework to assess perceived susceptibility to and severity of a disease, perceived benefit of engaging in a health behavior, and perceived barriers to performing this behavior. This study, part two of a larger three part project, examines the health beliefs of 44 adult females diagnosed with Fabry disease from across the United States through the means of a concurrent demographic survey and written, multiple choice and open-ended health belief questionnaire. Themes emerging from analysis of part one of the larger three part project, aimed at describing the health beliefs of ten females through qualitative thematic analysis, informed the design of the health belief questionnaire utilized in this study. This study characterizes the health beliefs of a larger population of adult females diagnosed with Fabry disease than previously assessed in part one of the study, specifically assessing the perceived severity, perceived susceptibility, and perceived benefits of and barriers to treatment, evaluation,

and monitoring, and identifies strategies to address identified barriers, modifying variables, and cues to action to improve communication between healthcare providers and their female patients. Strategies developed to identify and address these barriers may be applied to other populations of females diagnosed with genetic conditions in which poor compliance for recommended evaluations and monitoring have been documented, providing a broader application and public health significance to the findings of this study.

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PREFACE

I would like to take this opportunity to sincerely thank my thesis committee members for their time, patience, flexibility, and overall support in the formation and completion of this project. I am forever grateful to Katie Long, Nadene Henderson, Michelle Graham, and Dr. David Finegold for a fabulous experience at the Lysosomal Storage Disorders Program at the Children's Hospital of Pittsburgh. Thank you so much for the phenomenal opportunities and kind support you provided me throughout my time at the University of Pittsburgh. I would like to extend a special thank you to Katie Long for her mentorship and guidance for the past two years. So much of what I have learned has come from your time and dedication. I am inspired by your passion and thrilled to be entering the world of lysosomal storage disorders having learned so much from you. I would like to thank Dr. John Shaffer for his willingness to help with this project on every possible level and for his selfless availability. I am so very grateful to Betsy Gettig and Robin Grubs for their support throughout my time within the genetic counseling program and for their guidance throughout the development and completion of this project.

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1.0 INTRODUCTION

The Lysosomal Storage Disorders (LSD) Program at the University of Pittsburgh and the Children's Hospital of Pittsburgh of UPMC is devoted to the care of individuals and families affected with and by lysosomal storage disorders. David Finegold, MD and genetic counselor Katie Long, MS, CGC work in collaboration to provide comprehensive disease management to individuals diagnosed with lysosomal storage disorders, including an X-linked lysosomal disorder called Fabry disease. Fabry disease is caused by a deficiency of the enzyme α -galactosidase and accumulation of the substrate globotriaosylceramide (GL3) in the vascular endothelial cells. Progressive GL3 accumulation leads to chronic, progressive multisystemic disease and end organ damage requiring management and monitoring from a team of specialists.¹⁻⁴ Females heterozygous for *GLA* mutations were previously thought to be asymptomatic and not at-risk for the development of disease manifestations.⁵ It has since been demonstrated and accepted among the medical community that heterozygous females can be affected with the full spectrum of Fabry disease symptoms, although females typically have a more variable disease presentation when compared to affected males.⁶

Female heterozygotes are at risk to suffer from significant multisystemic disease and should be monitored and treated accordingly.⁵ Recommendations for disease monitoring consisting of annual or semiannual evaluations from a team of multiple specialists are similar for both males and females affected with Fabry disease. Currently, the only FDA approved treatment

clinically available in the United States for Fabry disease is enzyme replacement therapy (ERT) using agalsidase beta (Fabrazyme, Genzyme, Sanofi Inc.).⁷ While initiation of treatment for males is recommended by age 10 to 13 years of age regardless of disease burden, initiation of treatment for females is dependent on degree of disease symptomology.^{4; 8} The discrepancy in the management of females compared to males has the potential to result in miscommunication between patient and provider regarding disease severity and susceptibility, delayed treatment, and possible debilitating progression of disease.⁹

Dr. David Finegold and Katie Long developed a three-part project to further characterize the unique clinical experience and health beliefs of females diagnosed with or at-risk for Fabry disease based on family history in which this study is Part 2. The project was inspired by an observation made in the care of their female patients with Fabry disease, in which they noted that their heterozygous female patients were not usually evaluated in the clinical setting unless they presented with serious complications of the disease, regardless of recommendations by health care professionals for regular evaluation. This circumstance was consistent with the current medical literature, which noted that females generally denied the presence or risk to develop significant complications with their health and were more likely to attend genetic counseling and clinical evaluations with their affected sons and male relatives than for their own health care management.^{2;}
⁵ While it had been demonstrated that females had a unique clinical relationship with health care professionals and engaged in management differently than males, there was insufficient information as to the potential factors that could be preventing evaluation, monitoring and treatment and contributing to noncompliance.

In an attempt to better understand the health beliefs unique to females with Fabry disease, ten interviews among females over the age of 18 affiliated with the Lysosomal Program and a

confirmed diagnosis of Fabry disease or diagnosis based on family history were conducted and analyzed. This consisted of Part 1 of the three-part project. The investigators utilized the Health Belief Model as a framework to structure the aims of their study and the content of the interview questions. The Health Belief Model is a multi-dimensional model designed to assess and understand the failed acceptance of disease prevention and screening strategies among populations by assessing the perceived severity, perceived susceptibility, perceived benefits, perceived barriers, modifying variables, cues to action, and self-efficacy.¹⁰ Analysis of the ten interviews was completed using qualitative thematic analysis, an approach to analysis of qualitative data that enables the identification, analysis, and reporting of patterns (themes) within data.¹¹ This approach was utilized in order to gain a deeper understanding of females' personal health beliefs and to address the lack of literature assessing the views and unique experiences of females with Fabry disease.

Thematic analysis of the ten interview narratives suggested that participants generally believed that Fabry disease was a very serious disease. The majority identified it as life-threatening, but some expressed uncertainty with regard to severity of the disease among females or felt there was a delay in the seriousness for females due to later onset of disease symptoms. When making a comparison to males, some females identified the disease was equal in severity to males while others felt it was not as serious for females in comparison to males.

With regard to susceptibility to Fabry disease, participants demonstrated an appropriate understanding of the natural history of Fabry disease including the risk for renal, cardiac, and cerebrovascular disease among females with Fabry disease, but demonstrated a decreased personal susceptibility to Fabry disease manifestations. Some participants acknowledged that this was due to denial and an inability to emotionally handle the implications of being a symptomatic mother,

sister, daughter, or caretaker for a male relative who was also symptomatic. Therefore, subjects avoided thinking about their own personal risk. There were others, however, who expressed an inevitability to having complications of Fabry disease and likened themselves to family members who had died of kidney or cardiac disease. These women believed they were very susceptible to the symptoms of Fabry disease and expressed that they may not be able to change the outcome even with monitoring or treatment. Some believed that they would follow the family pattern of symptom expression and this either made them feel more susceptible or less susceptible to the symptoms of Fabry disease.

With regard to benefit of evaluations, monitoring, and treatment, participants generally indicated early intervention could be helpful to preventing later disease symptoms but also felt this could be delayed until significant symptoms were present. This may be linked to the themes of guilt and denial that cause some women to suppress their personal needs. Others thought evaluations and monitoring could be helpful in assessing response to enzyme replacement therapy and determining if it was helpful to them.

Themes regarding barriers to evaluations, monitoring, and treatment were both explicitly stated by participants and explored through the analysis of the interviews. Many participants' responses throughout the interviews were permeated by profound denial, grief, guilt, excessive worry, and sadness that influenced decision making related to engaging in routine evaluations, monitoring, and treatment. Concern for the health outcomes of male relatives was commonly reported and identified as the role of the caretaker. Guilt appeared to be a theme playing a role in several participant responses regarding the need to be a caretaker despite a rational recognition that the participant did not choose to pass on the disease and does not choose to be "well" while her male family member is "sick". There were also pervasive themes of duty and loyalty among

women with a symptomatic male relative. Subjects who described their role as a caretaker also talked about how this perspective is actively passed down through generations of women in the family. The theme of modeling the caretaker behavior and discouraging self-focus among female relatives was noted in several participant responses.

Table 1. Thematic analysis from Part 1: Barriers to evaluations, monitoring and treatment

| | |
|--|-----------------|
| Anger | Fear |
| Burden on family | Grief |
| Carrier terminology | Guilt |
| Concern for employment or insurance discrimination | Helplessness |
| Caretaker role: Duty, loyalty, discouraging self focus | Lack of support |

This current study, which is Part 2 of this project, utilized the themes described above that emerged from the transcripts in the aforementioned study (Part 1) to design a questionnaire to assess the health beliefs among a broader group of women diagnosed and at-risk for Fabry disease. The combined efforts of Part 1 and Part 2 will provide insight into the health beliefs of the Fabry female population with a specific interest is assessing barriers to engaging in preventative health behaviors and contributing to the development of strategies to address these barriers and improve patient compliance with recommended therapies.

1.1 SPECIFIC AIMS

The specific aims of this project are as follows: (1) to design and administer to 50 females at risk or diagnosed with Fabry disease a clinical questionnaire to assess (2) perceived severity of Fabry disease, (3) perceived susceptibility to Fabry disease manifestations, (4) perceived benefits to engaging in clinical evaluation, monitoring and treatment, and (5) perceived barriers to clinical evaluation, monitoring and treatment. Additionally, as a sixth aim, (6) this study will attempt to identify differences among these females that affect their health beliefs, including those women who are on and are not on enzyme replacement therapy.

1.2 BACKGROUND AND SIGNIFICANCE

1.2.1 Fabry Disease

Fabry disease is an X-linked lysosomal storage disorder that affects both males and females and results from a deficiency or absence of the enzyme α -galactosidase that leads to the progressive accumulation of globotriaosylceramide (GL3).¹² Virtually any organ may be affected by Fabry disease with disease manifestations affecting the renal, cardiac, neurologic, cerebrovascular, gastrointestinal, ophthalmologic, and dermatologic systems.¹⁻³ Fabry disease has no ethnic predilection and has an estimated incidence of 1 in 40,000 to 117,000 based on clinical ascertainment.^{6; 12; 13} Recent data from newborn screening initiatives and screening of high risk populations, however, suggests that the incidence may be greater than originally predicted. The incidence from international efforts of newborn screening is estimated to range from 1 in 1,250 to

1 in 3,859.¹⁴⁻¹⁷ Studies have also found an increased incidence of Fabry disease, ranging from 1 in 20 to 1 in 1,000, within high-risk populations including patients with cryptogenic strokes, hypertrophic cardiomyopathy, and those initiated on renal dialysis.^{18; 19}

1.2.1.1 Molecular Genetics and Pathogenesis

Fabry disease is caused by mutations in the gene *GLA* located on Xq22.1. More than 431 mutations have been identified in *GLA*, the majority of which are private mutations.¹² As the majority of mutations are unique to a specific family or individual, the genotype is generally not an accurate predictor for disease course or severity.⁶ Pathogenic mutations result in deficiency or absence of the enzyme α -galactosidase A, which functions to break down glycolipids within the lysosome. The enzyme deficiency results in the progressive accumulation of the substrate GL3 within the lysosomes of the cells in most organs, leading to cellular damage and organ dysfunction. GL3 accumulation is targeted within the glomerular and tubular epithelial cells of the renal system, the myocardial cells and valvular fibrocytes of the cardiac system, neurons of the dorsal root ganglia of the autonomous nervous system, and the epithelial, perithelial, and smooth muscle cells of the vascular system.¹²

1.2.1.2 Clinical Course of Fabry Disease

Fabry disease is a chronic progressive condition with multisystemic disease resulting from lysosomal GL3 accumulation. Although it was originally believed that females were not at risk to develop disease features, it is now accepted that female heterozygotes can be affected with Fabry disease symptoms. The presentation and severity of manifestations of Fabry disease can differ between males and females, with females typically having a wider spectrum of disease severity presumably due to X-inactivation.⁶ Symptoms often begin in childhood, with the average age of

disease onset in males ranging from 6-8 years of age and an average age of disease onset in females of 9 years of age. Of note, there is great variability of disease presentation between individuals diagnosed with Fabry disease, even between individuals within the same kindred.^{20; 21 22}

Fabry disease manifestations involve the renal, cardiac, neurologic, cerebrovascular, gastrointestinal, ophthalmologic, and dermatologic systems, with significant morbidity and mortality attributed to progressive renal insufficiency, central and peripheral nervous system disease, and cardiovascular disease.^{2; 3; 23} Renal and cardiac diseases typically present in the second to third decades of life, but have been documented in affected individuals as early as childhood.^{20; 22} Renal manifestations include proteinuria, hypertension and chronic renal insufficiency. End stage renal failure presents in approximately 31% of males and 1-4% of females, which can result in interventions including renal dialysis or renal transplantation. Cardiac disease includes conduction and valvular abnormalities, arrhythmias, cardiomyopathy, and left ventricular hypertrophy. Untreated cardiac manifestations can result in life threatening complications such as myocardial infarction and congestive heart failure. Additionally, storage of GL3 within the vascular system increases the risk for severe manifestations including transient ischemic attacks (mini strokes) and strokes in individuals with Fabry disease.^{2; 3; 19; 24-28}

Neuropathic pain and gastrointestinal symptoms such as diarrhea, constipation and abdominal cramping are significant sources of burden that can contribute to poor quality of life for Fabry patients. Pain consists of acroparesthesias (constant burning and tingling) particularly in the hands and feet, as well as episodic pain crises of severe, sharp neuropathic pain.²⁹ Both symptoms begin in childhood and are the most common presenting symptoms for a person diagnosed with Fabry.^{20 19; 22} Additionally, individuals with Fabry disease suffer from other multisystemic symptoms including angiokeratoma, tinnitus, hearing loss, corneal whorls, vertigo,

obstructive pulmonary disease, and psychological conditions such as panic attacks, depression and adaptive functioning disorders.^{2; 3; 12; 19; 24-26; 30; 31}

Men and women diagnosed with Fabry disease have a shortened lifespan compared to their healthy counterparts. The median age of death for men with Fabry disease is 58.2 years of age, which represents an approximate 16.5-year reduction of lifespan from the male general population. Women with Fabry disease typically have a more variable presentation and older age of onset than affected men. The life expectancy for women with Fabry disease is approximately age 75.4, which is on average 4.6 years younger than the female general population.³² Life expectancy for males and females after treatment with enzyme replacement therapy has not yet been assessed; although it is suspected that the life expectancy would be improved.¹²

1.2.1.3 Inheritance and Recurrence Risk

Fabry disease is inherited in an X-linked manner.¹² Previously it was believed that women were not at risk to develop disease manifestations, consistent with an X-linked recessive manner of inheritance. Females with a *GLA* mutation were presumed to be unaffected and were labeled “carriers” of Fabry disease. It has since been demonstrated that women are at risk to develop potentially all of the symptoms of Fabry disease, including serious manifestations such as stroke, renal failure, and cardiac disease. It is recommended that women with a *GLA* mutation be called “heterozygotes” and not “carriers” to prevent incorrect assumptions that females are not at risk for disease symptoms.^{6; 33; 34} Heterozygous women with Fabry disease have a 50% chance with each pregnancy to pass on the mutation for Fabry disease and have either an affected son or daughter who would be at risk for Fabry disease symptoms. There is no male to male transmission of Fabry disease, but all daughters of affected men will inherit the mutated gene.¹⁹

1.2.1.4 Diagnosis

Fabry disease is difficult to diagnose clinically as the symptoms are diverse and nonspecific, involve multiple organs, and can be easily confused with other pathologies. Consequently, affected individuals can experience a “diagnostic odyssey” resulting in an average of ten years of medical care with ten different medical specialists before receiving a confirmatory diagnosis of Fabry disease.⁶ Females with Fabry disease have an average 16.3-year delay in diagnosis from symptom onset.³⁵ Suspicion for Fabry disease most often comes from nephrologists, dermatologists, ophthalmologists or geneticists.⁶

When Fabry disease is suspected in an individual, confirmation of diagnosis is ascertained using different methods for males and for females. Confirmation of diagnosis for hemizygous males with a suspicious family and/or medical history of Fabry disease is made by demonstrating absent or reduced α -galactosidase A enzymatic activity in blood leukocytes and/or plasma or by sequencing of the *GLA* gene. Diagnosis of heterozygous females is not based on enzyme analysis as women can have low or normal enzyme activity, leading to inconclusive results. Direct sequencing of the gene *GLA* followed by deletion/duplication studies is the only reliable method to confirm diagnosis in suspected females.^{6; 12; 19}

The construction and interpretation of a targeted family history identifies at-risk family members and is an effective and efficient means for diagnosis of Fabry disease. On average there are at least five family members who are diagnosed with Fabry disease after the initial proband is diagnosed.³⁶ Typically, the initial proband will be male, however, subsequent diagnoses made from that initial diagnosis often result in the identification of heterozygous females with a more variable presentation of disease.^{6; 19}

1.2.1.5 Disease Management and Treatment

Management of Fabry disease requires a comprehensive, multidisciplinary approach ideally conducted by medical specialists with experience treating its manifestations. The number of body systems affected by the disease necessitates the involvement of multiple specialists in the care of an individual with Fabry disease. Clear communication between these different medical professionals is essential to an effective team approach to disease management. Comprehensive monitoring, regardless of age, sex and treatment status, should be conducted on a semiannual to annual basis and include monitoring by the following: nephrologists, cardiologists, neurologists, audiologists, ophthalmologists, pulmonologists, gastroenterologists, psychologists, and geneticists.^{4; 19; 24} Guidelines have been proposed by Eng et al. 2006 to manage both males and females diagnosed with Fabry disease (Table 2).⁴

Table 2. Proposed assessments in Fabry disease patients, (adapted from Eng et al. 2006)⁴

| Organ System | Assessment | Intervals and/or Indications |
|---------------------|---|--|
| General | General status, school or work performance, mental health | Baseline (at first visit), every 6 months |
| | Complete physical examination, assessment of quality of life | |
| | Genetic Counseling | |
| | Genotype | If not previously determined |
| Kidney | Serum electrolytes, creatinine, BUN; 24 hour urine or spot urine for total protein/creatinine, albumin/creatinine, sodium, creatinine, and (optional) GL-3 | Baseline. Every 3 month to every 12 mos. depending on the stage of chronic kidney disease (CKD) |
| Cardiac | Palpitations, angina | Baseline, every 6 months |
| | Blood pressure, rhythm | Every evaluation visit |
| | Electrocardiography and echocardiography | Baseline. Every 2 years for patients ≤35 years, every year thereafter |
| | 30-day holter monitoring | If an arrhythmia is suspected or palpitations are present |
| | Cardiac MRI | Optional |
| Neurologic | Acroparesthesias, fatigue, fever, sweating, heat and cold intolerance, joint pains, stroke-related symptoms, TIA | Baseline, every 6 months |
| | Neurologic exam, Pain assessment | Baseline, every 6 months |
| | Brain MRI without contrast | Baseline. If TIA or stroke event In females to document CNS involvement |
| | Comorbid stroke risk factors: Cholesterol (Total, LDL, HDL), triglycerides, Lipoprotein A, total plasma homocysteine, factor V Leiden (G1691A), Protein C, Protein S, prothrombin G20210A, antithrombin III, anticardiolipin, lupus anticoagulant | Baseline Every 12 months |
| ENT | Tinnitus, hearing loss, vertigo, dizziness | Baseline, every 6 months |
| | Audiometry, tympanometry, otoacoustic emissions | Baseline, yearly thereafter |
| Ophthalmologic | Visual disturbances, light sensitivity | Baseline, every 6 months |
| | General ophthalmologic exam | Baseline, every 12 months |
| Pulmonology | Cough, exertional dyspnea, wheezing, exercise intolerance | Baseline, every 6 months |
| | Spirometry, including response to bronchodilators, treadmill exercise testing, oximetry, chest X-ray | Baseline, every 2 years or more frequently for clinical indications |
| Gastrointestinal | Postprandial abdominal pain, bloating, diarrhea, nausea, vomiting, early satiety, difficulty gaining weight | Baseline, every 6 months |

In 2003 the US Food and Drug Administration (FDA) approved agalsidase beta (Fabrazyme, Genzyme, Sanofi Inc) intravenous enzyme replacement therapy (ERT) for treatment of Fabry disease in both males and females. Individuals receiving ERT typically require intravenous administration of therapy once every two weeks, a procedure that in most instances

can eventually be moved into the home to be administered by a trained home care nurse. The decision to start treatment for an individual is largely based on clinical assessment, but is recommended to be initiated by age 10 to 13 years of age for affected males due to known natural history of untreated Fabry disease.⁸ In contrast to males, the decision to initiate ERT for females is dependent upon the presence of significant symptoms or progressive end organ involvement and not based on age. Specific symptoms and measurements of biomarkers for clinical manifestations have been outlined by Eng et al. to determine if and when a female should be initiated with ERT.⁴

Several studies have been conducted to better quantify potential clinical benefit from the administration of agalsidase beta. Clinical benefit of agalsidase beta has been demonstrated in multiple clinical trials by the effective reduction of plasma and tissue GL3 (a biomarker used to monitor disease progression) in the vascular endothelium of the kidney, skin and heart.³⁷⁻³⁹ Studies have also suggested that ERT decreases pain and improves quality of life for affected men and women.^{40; 41} There is debate among clinicians who manage patients with Fabry disease with regard to the timing of the initiation of ERT. A recent study suggested that the earlier ERT is begun the greater clinical benefit with regard to renal disease. This recommendation is based on findings that long-term ERT use in young patients (as young as age 7) results in complete clearance of GL3 in the mesangial and glomerular endothelial cells of the kidney with dose dependent clearance of the renal podocyte inclusions.⁴² The study population consisted of eleven males and one female and had a median age of 16.5 years with an age range of 7 to 33. Still, some physicians believe that mindful watching is preferable to presymptomatic initiation of treatment. Although evidence suggests ERT provides some degree of clinical benefit to men and women with Fabry disease, treatment does not reverse or completely prevent end organ damage. Adjunctive therapies, specifically for proteinuria, hypertension, stroke prevention, gastrointestinal distress, and

depression, and disease monitoring are still indicated when individuals are treated with ERT.¹² This means that current treatment options for Fabry disease do not necessarily decrease the number of tests or doctors visits required to manage disease features.

Psychosocial issues and demanding disease-monitoring recommendations have the potential to act as barriers to disease treatment, evaluation, and monitoring. Barriers to treatment with enzyme replacement therapy currently demonstrated in the literature include time constraints and conflicts with schedules, financial resources, medical insurance, fear and distrust of treatment, and risk of infusion reactions to ERT.⁴³ It is possible that fear and distrust of treatment was identified around the time of ERT development because there was a lack of experience with this treatment in the Fabry disease community. The research that examines barriers includes both males and females Fabry patients thus making it difficult to discern whether there might be barriers unique to females receiving ERT.

Although some degree of efficacy of treatment with ERT has been shown in the literature, long-term clinical benefits remain unclear especially with regards to stroke prevention.^{7; 44; 45} The high cost of lifelong treatment, potential for immune reactions, and the need for repeated administration of large amounts of enzyme may acts as burdens to Fabry disease patients. In addition, this methodology of treatment is unable to cross the blood brain barrier and treat neurologic complications.⁷ Efforts are currently being made to provide alternative treatments for Fabry disease in the United States including substrate reduction therapy, residual enzyme activators, chemical chaperone therapy, *GLA* promoter activity, protein homeostasis regulation, next generation ERT, and gene therapy. A number of treatments are still in the early forms of research and development. However, one form of substrate reduction therapy (Amicus, AT1001) is currently being studied in phase III clinical trials. Substrate reduction therapy is designed to

stabilize the naturally occurring enzyme in individuals and is suspected to increase enzyme activity.^{7; 12; 38; 46; 47} Additional and/or improved treatments have the potential to improve the care and quality of life of individuals with Fabry disease.

1.2.2 Psychosocial Issues Associated with Fabry Disease

Individuals with Fabry disease are at an increased risk for mental health issues as compared to the general population. Depression and anxiety have been cited as both clinical features and psychosocial issues associated with Fabry disease. Originally thought to be a secondary complication from chronic disease, depression and anxiety were accepted as primary disease complications in 2002 with the discovery of white matter changes in the brain detected by magnetic resonance imaging (MRI). Depression and anxiety as a result of white matter disease is thought to be exacerbated by secondary complications including unpredictability of pain and gastrointestinal symptoms, increasing disability, and awareness of shortened lifespan.²⁹ Furthermore, psychological issues related to a genetic diagnosis in general may further complicate the mental health of an individual with Fabry disease including denial, anxiety, anger, grief, survivor and parental guilt, blame, depression, isolation, inability to cope, hopelessness, damage to self-esteem, changed relationship with family of origin, and change in sense of identity.²⁴

Studies of psychological dysfunction and mental health impairment have largely been conducted in affected males to date. The rates of depression, marital problems, unemployment, and suicide are higher in males with Fabry disease in comparison to their healthy counterparts.^{2; 24} Disfiguring angiokeratomas can be a significant source of embarrassment and distress for individuals with Fabry disease. Additionally, angiokeratomas located on the genitalia as well as

symptoms including chronic pain and fatigue may serve as barriers to the initiation and continuation of sexual relationships.^{3; 24; 26}

More recent initiatives to evaluate the psychological aspects of Fabry disease have attempted to examine populations of both males and females affected with Fabry disease. Crosbie et al. 2009 evaluated the psychological functioning of 28 males and females with Fabry disease using the Minnesota Multiphasic Personality Inventory (MMPI-2), a measure widely used in chronic illness and chronic pain populations. Both males and females with Fabry disease were found to have significant psychological distress and a pessimistic attitude toward the future. In addition, these individuals demonstrated increased suspiciousness of others, which could result in increased apprehensive behavior, anger, and resentment. The results of the study suggested that individuals with Fabry disease isolate themselves from others, may express defensiveness, and have the potential to minimize psychopathology when confronted about their mental health. When compared to chronic pain patient populations, Fabry disease patients scored comparatively on the MMPI-2 scales, underscoring the physical suffering that Fabry disease patients feel.⁴³ Laney et al. 2009 examined the social-adaptive and psychological functioning of 33 males and females with Fabry disease using the *Diagnostic and statistical manual of mental disorders IV* (DSM-IV) criteria and various aspects of daily life. Patients with Fabry disease were found to have poorer adaptive functioning correlating with increased rates of depression, anxiety, depression and anxiety, antisocial personality, attention-deficit/hyperactivity, hyperactivity-impulsivity, and aggressive behavior. The study concluded that the neuropsychological impact of Fabry disease on the day-to-day activities of affected males and females is likely underappreciated by health care providers.³¹

1.2.3 Psychological Burden and Quality of Life among Female Heterozygotes

While recent measures have been taken to incorporate females into the assessment of Fabry disease burden including psychological functioning and quality of life, few studies have focused solely on the unique concerns of affected females. A large-scale assessment of 202 females with Fabry disease was completed in 2006 by Street et al. to delineate the quality of life among heterozygous females. Females within this population were found to have decreased quality of life compared to a control population from the Women's Health Initiative, a large prospective study of postmenopausal women with the goal of identifying health behaviors, disease predictors, and approaches to disease prevention. Females with Fabry disease were also found to have decreased emotional health, energy and general health when compared to a population of men and women with rheumatoid arthritis and increased pain and burden of disease when compared to a population of men and women with multiple sclerosis.⁴⁸ In 2007 Wang et al. confirmed within a population of 44 affected females the prevalence of an overall reduced quality of life, but found this reduction was due to fatigue, exercise intolerance, and poor self-perception of health. In addition to these factors, pain contributed to a high prevalence of depression and anxiety for study participants.⁵ While these studies provide evidence that females have significant psychological distress and burden from Fabry disease, further studies are needed to more comprehensively understand the experience of heterozygous females and to differentiate potential psychosocial differences between affected males and females.

1.2.4 Barriers to Healthcare for Female Heterozygotes

In 2008 Gibas et al. hypothesized that females with Fabry disease experienced unique barriers to healthcare and treatment due to a “triple disadvantage” from disease rarity, devalued carrier status, and gender. In the analysis of 51 females with Fabry disease it was noted that females have a history of being labeled less credible, more problematic patients when compared to males and that labeling females as asymptomatic carriers may cause them to be ignored, dismissed, and disbelieved by some healthcare professionals. Gibas et al. argues for the critical role of genetic counselors as advocates for women with Fabry disease to health care providers to help mitigate the potential consequences of problematic interactions between providers and patients.⁹ While this study provides valuable insight into potential barriers for females, this study is limited by the scope of the study design, which included a questionnaire asking participants about their experiences only with neuropathic pain and not explicitly about their experiences with healthcare professions. The authors of this study recommend future studies incorporate personal interviews with female heterozygotes to gather more specific information about interactions with and barriers to healthcare.

1.2.5 The Health Belief Model

The Health Belief Model is a multi-dimensional model defined in the 1970s to assess and understand the failed acceptance of disease prevention and screening strategies among populations.¹⁰ This model incorporates assessments including an individuals’ perceived susceptibility to a disease/condition, perceived severity of the disease/condition, perceived benefit of engaging in a health behavior, and perceived barriers to performing this behavior.⁴⁹

Comprehensive review of this model after ten years of use by researchers found that perceived barriers is the most powerful of the dimensions in the Health Belief Model. Perceived susceptibility was determined to be a significant contributor to engaging in preventive health behaviors while perceived benefit was also a significant contributor but to a lesser degree. Perceived severity was found to be only weakly associated with preventive health behaviors.¹⁰

In 1988 self-efficacy was added to the four components of the Health Belief Model. Self-efficacy refers to an individual's perception that he or she is competent to successfully perform a behavior and is a key component of health behavior change.⁵⁰ The Health Belief Model suggests that individual characteristics act as modifying variables that indirectly affect health-related behaviors by impacting perceived severity, perceived susceptibility, perceived benefits and perceived barriers. Modifying variables can include demographic, psychosocial, or structural variables. Psychosocial variables include personality, social class, and pressure from peer groups. Structural variables include prior knowledge and/or contact with a disease, among other variables.⁵¹ In addition, the Health Belief Model theorizes that a trigger, or a cue to action, is necessary for prompting engagement in health behaviors. Cues to action may be internal, such as physiological symptoms, or external, such as information from media or healthcare providers.¹⁰

There is extensive literature on the Health Belief Model and a complete review of the literature is beyond the scope of this thesis. However, the Health Belief Model has been utilized to study issues related to genetic diagnoses and genetic counseling. For example, the Health Belief Model has been used to study issues such as uptake of genetic testing, compliance with recommended management, and the effectiveness of genetic counseling.⁵²⁻⁵⁶ Characterization of the health beliefs of individuals with genetic conditions has led to the development of strategies to improve patient compliance and patient communication with health professionals.^{52; 55; 56} Multiple

studies have examined aspects of genetic testing, genetic counseling, and recommended management for individuals with genetic predispositions to both breast and colorectal cancer using the Health Belief Model as a framework.⁵²⁻⁵⁴ Assessment of the health beliefs of individuals within these populations has aided in the development of strategies to improve decision-making with regard to genetic testing and to provide more effective genetic counseling strategies within cancer genetics.⁵²⁻⁵⁴ The Health Belief Model has also been utilized to improve prenatal genetic counselors' facilitation of the decision-making process for the utilization of amniocentesis, an invasive procedure performed during pregnancy to provide chromosomal analysis of the fetus, for females of advanced maternal age.⁵⁵ Finally, the Health Belief Model was successfully employed in 2007 by Gustafson et al. as a means to assess poor understanding of disease prevention and screening for African American females with sickle cell disease, an autosomal recessive genetic condition prevalent in individuals of African American ethnicity.⁵⁶

1.2.6 Qualitative Research

1.2.6.1 Qualitative Research Methods

A review of the literature revealed only two studies that assessed the psychological burden unique to females with Fabry disease, both of which utilized a quantitative approach. While these studies provide valuable information regarding the unique psychosocial concerns of females with Fabry disease, however they do not allow the researcher to characterize issues that may be unanticipated or considered important by the participants. Qualitative descriptive analysis, however, enables investigators to discover and document aspects of reality that cannot be anticipated, making it a particularly effective approach to characterize a minimally explored circumstance such as the health beliefs of females with Fabry disease.⁵⁷

Qualitative descriptive studies aim to study the world from the perspective of an individual. This research methodology is often about exploring meaning, attempting to explain what people do and why they do it.⁵⁷ Description from this analysis, largely gathered from open ended questions, is particularly effective in obtaining answers to questions of relevance to practitioners, such as physicians or genetic counselors.⁵⁸ Healthcare providers can use information gathered from qualitative analysis to improve their interactions with patients and reduce miscommunication. Furthermore, this analysis provides a description of events in the everyday terms of those events, meaning the conclusions from a study can reflect the experience of a participant in his or her own words.⁵⁷ This in turn allows for healthcare providers to explore and address potential barriers and burdens for their patients in a more effective way, utilizing the language patients use themselves.

1.2.6.2 Thematic Analysis

Thematic analysis is a type of qualitative analysis that enables the identification, analysis, and reporting of patterns (themes) within data. A theme is defined as a pattern that captures something important about the data in relation to the research question and represents some level of meaning within the data set. Thematic analysis allows for either the rich description of a broad research question or a more nuanced and complex description of a particular theme.¹¹ Both applications of thematic analysis allow for the ability to characterize unexplored circumstances that may not have been addressed in the literature. In addition, this approach is a relatively quick and easy technique for new researchers to learn and can be used under a number of qualitative theoretical frameworks, making it a flexible and comprehensive framework in which to perform qualitative analysis. A drawback to thematic analysis, however, is that the methodology is not well described and is open to interpretation.¹¹

2.0 EXPERIMENTAL DESIGN AND METHODS

The study design was originally approved by the University of Pittsburgh's Institutional Review Board (IRB) on, August 11, 2010 and renewed yearly with the most recent renewal on May 22, 2013 (Replications of IRB Approval letters for protocol # REN11070017/PRO10060403 can be found in Appendix A). This study was funded by Genzyme, a subsidiary of Sanofi.

2.1 PARTICIPANT RECRUITMENT

This study was designed to recruit females over the age of 18 who were diagnosed with or at-risk for Fabry disease based on family history. Hospital and clinic sites with a known Fabry disease patient population from across the United States of America were contacted to distribute participant recruitment flyers (Appendix B) to adult females diagnosed or at-risk for Fabry disease within their care. Of those contacted, 14 clinical sites (Table 3) specializing in Fabry disease agreed to distribute the flyers to their adult female patients. Interested participants contacted the Principle Investigator (PI), Katie Long, by phone or email and were consented over the phone by the PI or other approved investigators using a telephone script (Appendix C). Participants who agreed to participate in the study were then mailed the demographic survey, clinical questionnaire, and a pre-paid, addressed envelope to mail the completed materials back to the PI. It was decided not to use electronic survey methods as a means for participants to complete the materials to prevent the exclusion of potential participants without computer or internet access. Upon receipt

of the completed demographic surveys and clinical questionnaires participants were mailed a \$20 debit card and a thank you flyer (Appendix D) in appreciation for their participation.

Table 3. Participating Hospital and Clinic Sites

| | |
|--|--|
| <i>Cedars Sinai</i> (Los Angeles, CA) | <i>Indiana University</i> (Indianapolis, IN) |
| Children's Hospital of Philadelphia (Philadelphia, PA) | Ann & H. Robert Lurie Children's Hospital of Chicago (Chicago, IL) |
| Children's Mercy Hospitals and Clinics (Kansas City, MO) | Massachusetts General Hospital (Boston, MA) |
| Children's Hospital of Pittsburgh (Pittsburgh, PA) | Northwest Oncology and Hematology (Coral Spring, FL) |
| Children's Hospital of Wisconsin (Milwaukee, WI) | University of Colorado Hospital (Aurora, CO) |
| Cincinnati Children's Hospital (Cincinnati, OH) | University of Washington (Seattle, WA) |
| Emory Genetics (Atlanta, GA) | Weiskopf Child Evaluation Center (Louisville, KY) |

2.2 DEMOGRAPHIC SURVEY

Each participant was asked to complete a survey designed to characterize demographics and information about the individual's family history of Fabry disease (Appendix E). The survey was designed to take approximately five to ten minutes and consisted of twelve questions. Information gathered from the administration of this survey was compiled using Microsoft Excel.

2.3 QUESTIONNAIRE

Participants were asked to complete a clinical questionnaire designed to elicit their health beliefs including: perceived severity of Fabry disease, perceived susceptibility to Fabry disease, and perceived benefits and barriers to treatment, evaluation and monitoring (Appendix F). Questionnaires were designed to take approximately twenty minutes and consisted of twelve questions designed in a multiple choice, binary yes or no, checklist, or open ended format. The results from the thematic analysis from Part 1 of this project were used to design the content of the questionnaire. Information gathered from the administration of this questionnaire included both quantitative and qualitative data. Analysis of the data included the use of Microsoft Excel and thematic analysis, respectively.

2.4 QUANTITATIVE ANALYSIS

Data from the demographic surveys and questionnaires including the multiple choice and checklist questions were compiled using Microsoft Excel. Descriptive statistical analysis was performed using Microsoft Excel. Further statistical analysis comparing variables for statistical significance was completed using R software. Analyses included McNemar's test of homogeneity, Logistic Regression, Fisher's exact test, Friedman's test, and the Wilcoxon test. P-values were adjusted, as needed, using the Bonferroni correction (α/N) for multiple comparisons.

2.5 QUALITATIVE ANALYSIS

Data from the open ended questions in the clinical questionnaires were transcribed into an electronic format using Microsoft Word. Transcripts adhered to participants' grammar and spelling. Thematic analysis of the open ended responses were completed using guidelines proposed by Braun et al. (2006). All transcripts were read by the author prior to the coding of the data in order to gain an appreciation of the scope of the data set. In addition, a comprehensive literature review, as summarized in the Background and Significance section, was completed prior to analysis. Thematic analysis can be conducted in either an inductive or theoretical manner. Inductive analysis generates a more data driven analysis and is particularly effective with regard to a research question that has little data in the literature. Theoretical thematic analysis, however, is more explicitly analyst-driven and is derived from pre-existing theories or preconceptions of the researcher from the literature.¹¹ Inductive thematic analysis was utilized in this study. Codes based on initially noted interesting features were generated and applied to the data in a systematic fashion. Codes were collated into potential themes and the corresponding responses were reviewed for congruency. Themes identified in the data set can either be semantically or latently derived. A semantic approach identifies themes within the explicit or surface meanings of data, whereas a latent approach involves interpretation of a deeper, underlying meaning to the theme.¹¹ Both approaches were appropriate for the generation of themes from the open ended responses and were utilized in the analysis to provide a thorough description of the data. Potential themes were refined and finalized based on continued review of and comparison to the raw free-response data, literature review, and the specific aims of the study.¹¹

3.0 RESULTS

3.1 DEMOGRAPHICS

A total of 44 females diagnosed with Fabry disease completed the survey and questionnaire. The average age of participants was 49 years with a median age of 50 years and an age range of 26 to 73 years. Of those females, 100% were White and one individual indicated she was both White and American Indian/Alaska Native. All of the participants (100%) were diagnosed with Fabry disease. The majority of participants made a total household income of \$35,000 or greater (71%) with the greatest percentage of participants indicating an income of greater than \$75,000 (32%). The educational background of the participants largely consisted of at least one to three years of college (32%) or four years or more of college (32%). When asked about marital status, approximately 23% of participants were single, 57% were married, 16% were divorced, and 5% were widowed. Approximately 50% of participants were employed (part time or full time), 95% had some form of healthcare insurance, and 18% could not go to the doctor within the last year due to healthcare costs (Table 4).

Table 4. Participant Demographics

| Demographics | % of subjects | Demographics | % of subjects |
|---------------------|----------------------|-------------------------|----------------------|
| Age | | Insurance Status | |
| Mean | 49 years | Insured | 95.45% |
| Median | 50 years | Uninsured | 2.27% |
| Range | 26-73 years | Unsure | 2.27% |

Table 4 Continued

| | | | |
|---|--------|---|--------|
| Race | | Employment | |
| Caucasian | 100% | Full or part time | 50.00% |
| American Indian, Alaska Native | 2.27% | Unemployed | 50.00% |
| Income | | Education: Highest Level | |
| <10,000 | 9.76% | Grade 8 or less | 0.00% |
| 10,000-20,000 | 9.76% | Grades 9-11 | 4.55% |
| 20,001-35,000 | 9.76% | Grade 12 or GED | 6.82% |
| 35,001-50,000 | 19.51% | College 1 yr-3 yr | 31.82% |
| 50,001-75,000 | 19.51% | College >4 yr | 31.82% |
| >75,000 | 31.71% | Graduate Level | 25.00% |
| Marital Status | | Prevention of healthcare due to cost | |
| Single | 22.73% | Yes | 18.18% |
| Married | 56.82% | No | 81.82% |
| Divorced | 15.91% | Diagnosed | |
| Separated | 0.00% | Yes | 100% |
| Widowed | 4.55% | No | 0% |
| N=44 | | | |
| *3 participants did not indicate income | | | |

3.1.1 Regional distribution of participants in the United States

Participant recruitment flyers were initially distributed to eight clinical sites: Emory Genetics, Massachusetts General Hospital, University of Washington, Ann and H. Robert Lurie Children's Hospital of Chicago, Weisskopf Child Evaluation Center, Cincinnati Children's Hospital, Children's Hospital of Wisconsin, and the University of Colorado Hospital. Participants were asked to indicate which of these centers managed their Fabry disease or to mark "Other" and write the center or clinic that managed their disease in the corresponding blank. Additional clinic sites were contacted for distribution of participant recruitment flyers. The percentages of participants from participating sites were as follows: Emory Genetics (12.5%), Massachusetts General Hospital

(4.6%), University of Washington (6.8%), Ann and H. Robert Lurie Children’s Hospital of Chicago (14.8%), Weisskopf Child Evaluation Center (6.8%), Cincinnati Children’s Hospital (11.4%), Children’s Hospital of Wisconsin (0%), the University of Colorado Hospital (2.3%), Cedars Sinai (2.3%), Children's Mercy Hospitals and Clinics (0%), Children's Hospital of Philadelphia (0%), Indiana University (4.6%), Northwest Oncology and Hematology (0%), and Children’s Hospital of Pittsburgh (6.8%) (Figure 1). Clinic sites listed by participants that were not participating clinic sites included the University of Utah, the Lysosomal Storage Disease Clinical Care Network, O&O Alpan, Dartmouth-Hitchcock Medical Center, primary care physician, Denver Nephrology, Mt Sinai Hospital, Central Dupage Hospital, and no current management of Fabry disease symptoms (Table 5). Centers providing management for participants were localized in regions using the Census Regions and Divisions of the United States (Appendix G). Participating sites and clinics listed by participants under “Other” were included in this analysis. Approximately 15% of participants were from the Northeast, 24% were from the South, 32% were from the Midwest, 16% were from the West, and 14% of participants were unable to be localized to a region either due to lack of current management or non-localizable management (Figure 2).

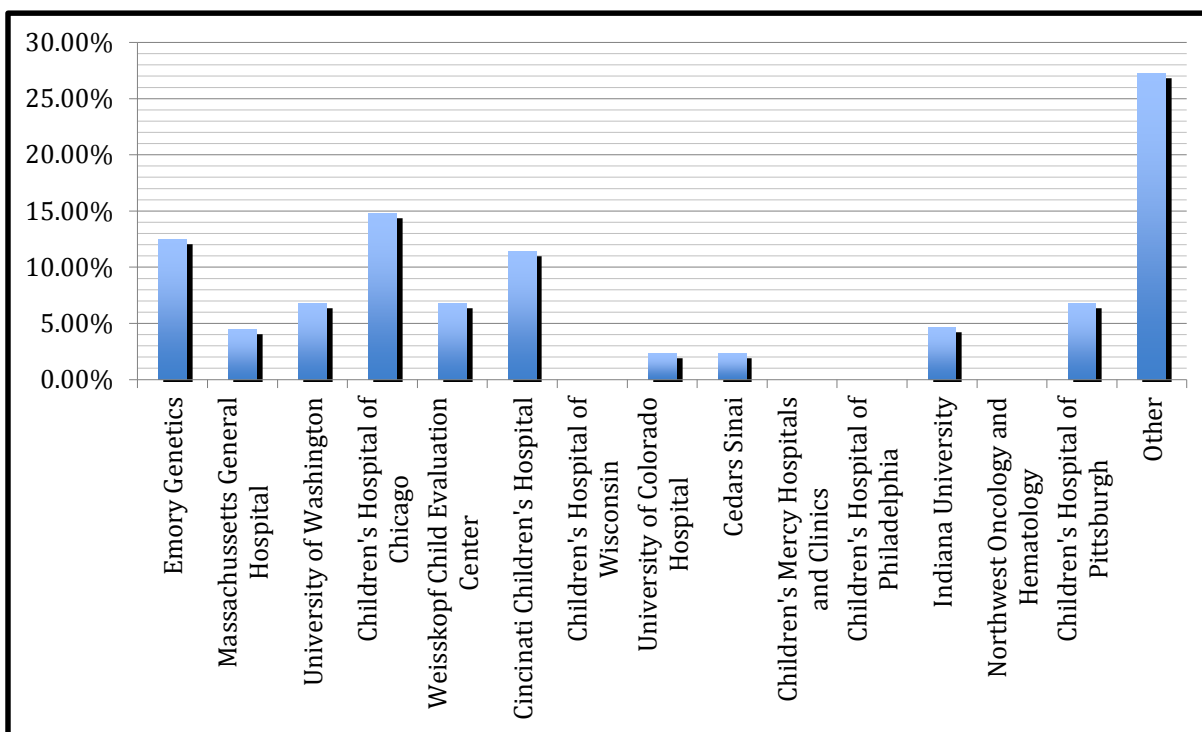


Figure 1. Proportion of participants managed at participating clinic sites (N=44)

Table 5. Clinic sites listed under “Other”

| Additional clinic sites | Percentage of subjects |
|--|------------------------|
| Currently none (n/a) | 4.5% |
| Lysosomal Storage Disorders Clinical Disease Network (n/a) | 2.3% |
| O&O Alpan (Fairfax, VA) | 2.3% |
| University of Utah (Salt Lake City, Utah) | 2.3% |
| Medical University of South Carolina (Charleston, SC) | 2.3% |
| Primary care physician (n/a) | 2.3% |
| Denver Nephrology (Denver, CO) | 2.3% |
| Dartmouth-Hitchcock Medical Center (Lebanon, NH) | 2.3% |
| Did not disclose (n/a) | 2.3% |
| Many years ago- through a blood test (n/a) | 2.3% |
| Central Dupage Hospital (Winfeild, IL) | 1.1% |
| Mt Sinai (New York, NY) | 1.1% |
| Total participants marked “Other” | 27.3% |

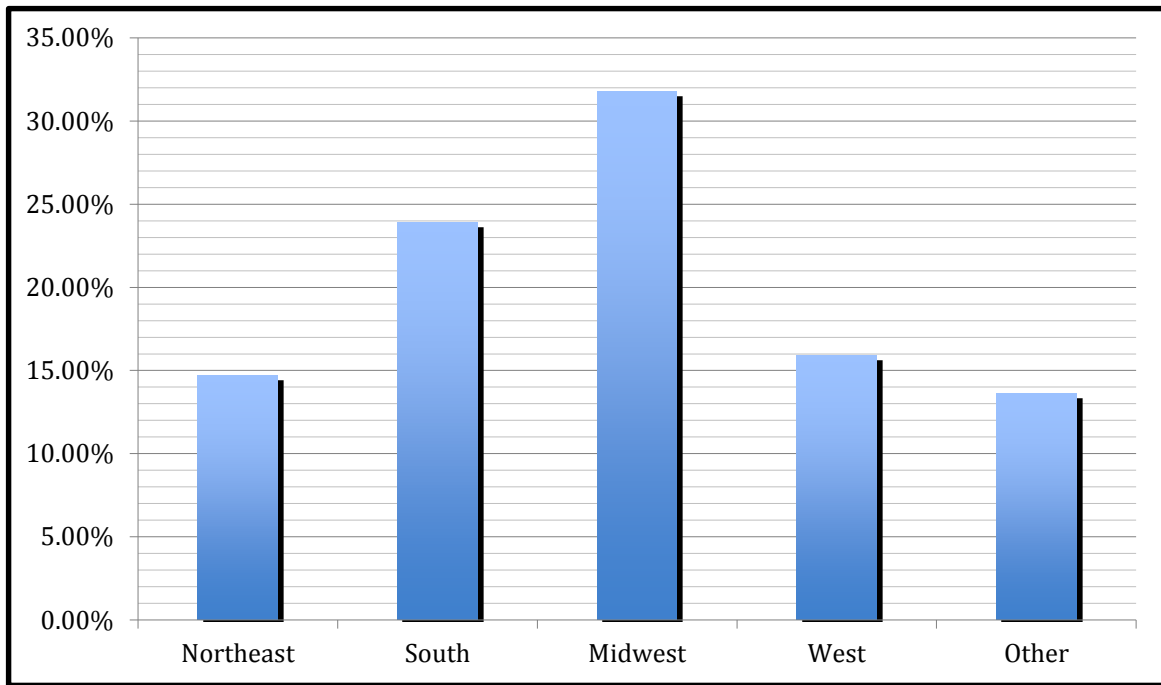


Figure 2. Distribution of Fabry disease managing clinic sites by region in the United States (N=44)

3.1.2 Family history of Fabry disease

The majority of participants (98%) had a family history of Fabry disease. Approximately 42% of participants had a son and/or daughter diagnosed with Fabry disease. Of the 43 participants who indicated a family history of Fabry disease, approximately 56% indicated maternally inherited disease, 40% indicated paternally inherited disease, and 4% marked relatives without a designated maternal or paternal inheritance (i.e. sister, brother, son, daughter, niece, nephew) (Figures 3-5). The most common relative indicated was mother, followed by sister, father, daughter, and son (Table 6).

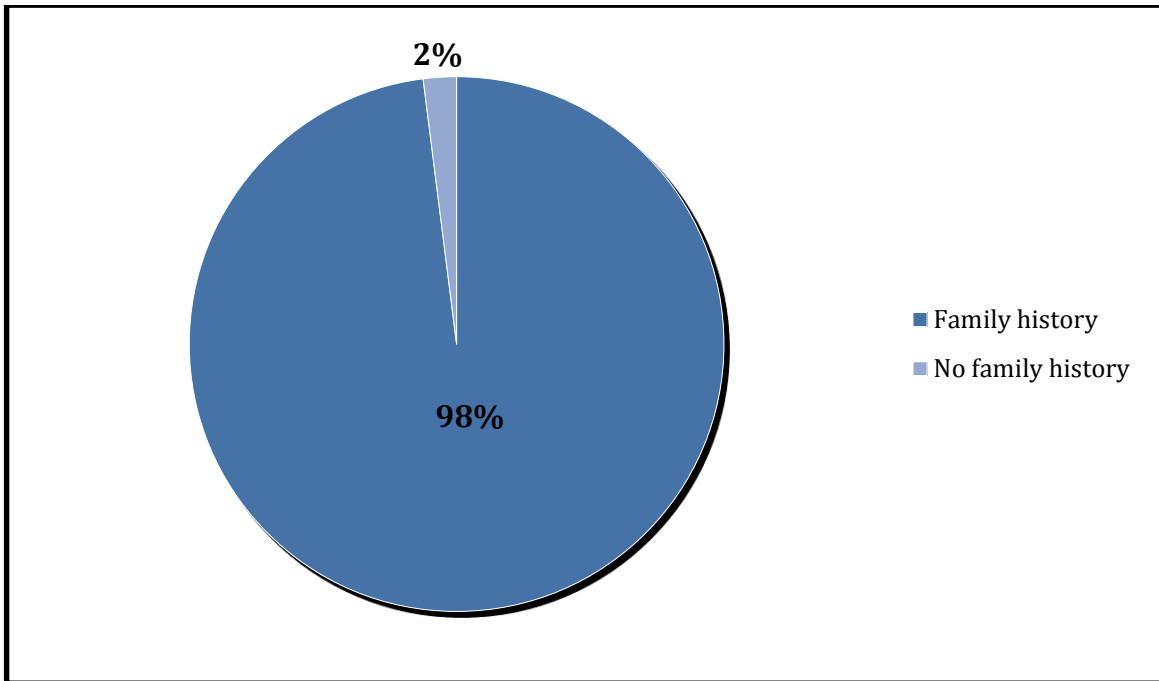


Figure 3. Proportion of participants with a family history of Fabry disease (N=44)

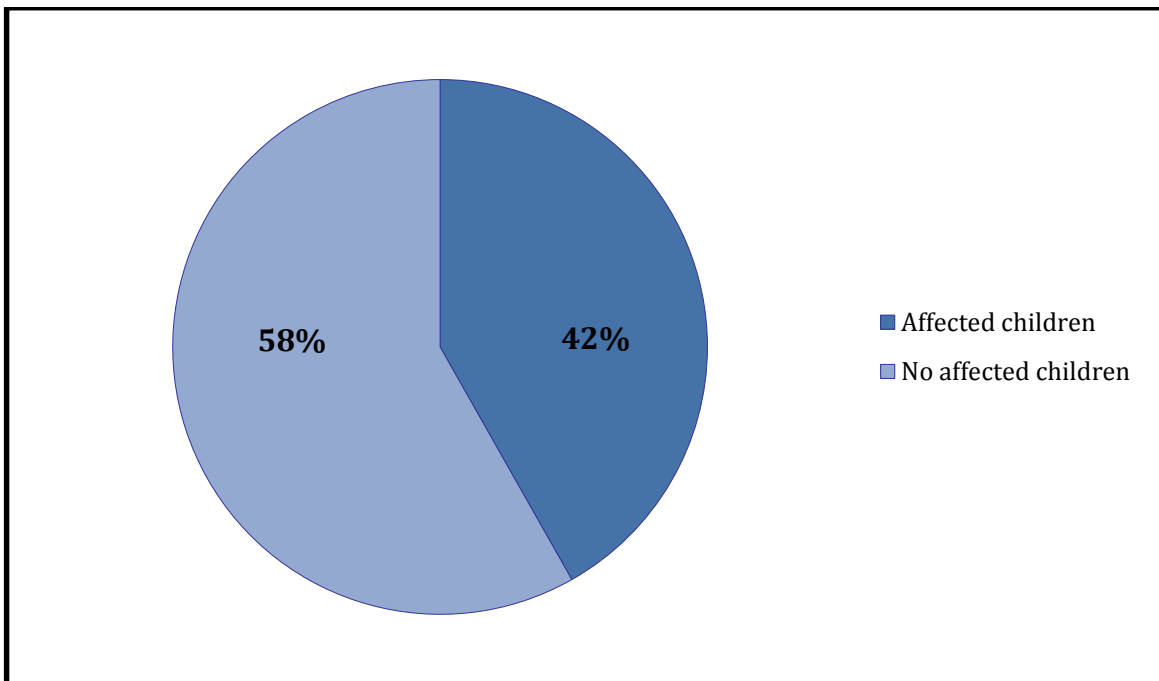


Figure 4. Proportion of participants with a son and/or daughter diagnosed with Fabry disease (N=43)

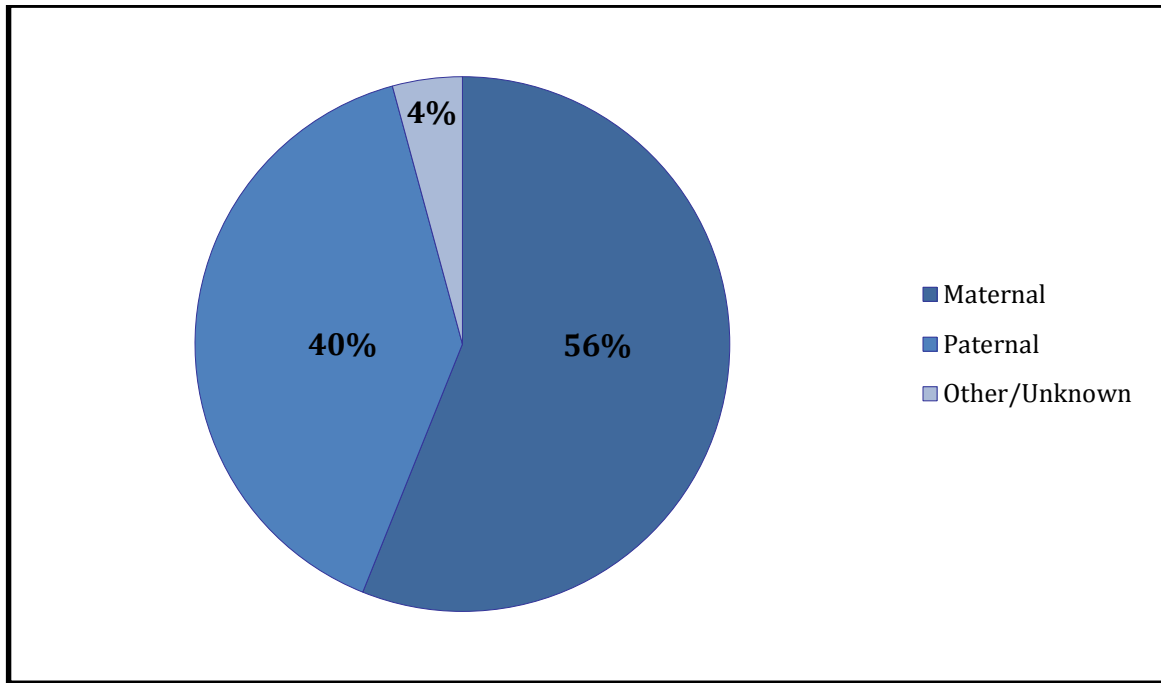


Figure 5. Origin of inheritance of Fabry disease (N=43)

Table 6. Percentage of individual relatives with Fabry disease (N=43)

| Relative | Percentage indicated by subjects |
|----------------------|----------------------------------|
| Mother | 46.5% |
| Sister | 41.9% |
| Father | 39.5% |
| Son | 37.2% |
| Daughter | 27.9% |
| Maternal Cousin | 27.9% |
| Brother | 23.3% |
| Maternal Aunt | 23.3% |
| Niece | 23.3% |
| Paternal Grandmother | 23.3% |
| Maternal Grandfather | 16.3% |
| Maternal Grandmother | 16.3% |
| Maternal Uncle | 16.3% |
| Paternal Uncle | 16.3% |
| Paternal Cousin | 16.3% |
| Nephew | 14.0% |
| Paternal Aunt | 9.3% |
| Paternal Grandmother | 0.0% |

3.1.3 Treatment of relatives with ERT

Of the 43 participants who indicated that they had a family history of Fabry disease, 86% had relatives who had been treated with ERT (Figure 6).

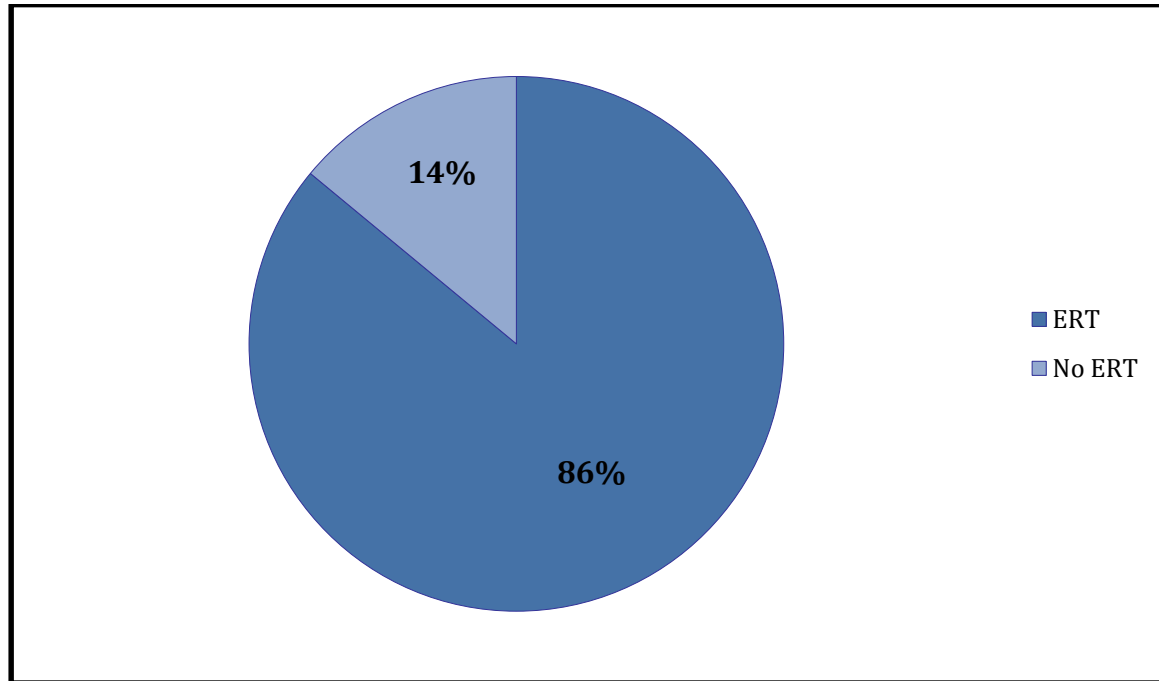


Figure 6. Percentage of participants' relatives treated with ERT (N=43)

3.2 SPECIFIC AIM TWO

3.2.1 Perceived severity

Participants were asked to categorize how serious Fabry disease was for males and for females.

Possible responses included:

- Fabry disease is very serious
- Fabry disease is somewhat serious
- Fabry disease can be serious, but is not always serious
- Fabry disease is not serious

The majority of participants, approximately 91%, indicated that Fabry disease was very serious for males. In contrast, approximately 48% of participants indicated that Fabry disease was very serious for females. For males, approximately 2% of participants indicated that Fabry disease was somewhat serious and 7% of participants indicated that Fabry disease could be serious, but was not always serious. For females, approximately 18% of participants indicated that Fabry disease was somewhat serious, and 34% of participants indicated that Fabry disease could be serious, but was not always serious. The p-value for this analysis was adjusted using the Bonferroni correction to a value of 0.02. Differences between the perceived severity for males and females were statistically significant as calculated by both the Friedman test (p-value of $7.74e^{-6}$) and the Wilcoxon test (p-value less than $2.2e^{-16}$). No participants (0%) indicated that Fabry disease was not serious for males or for females (Figure 7).

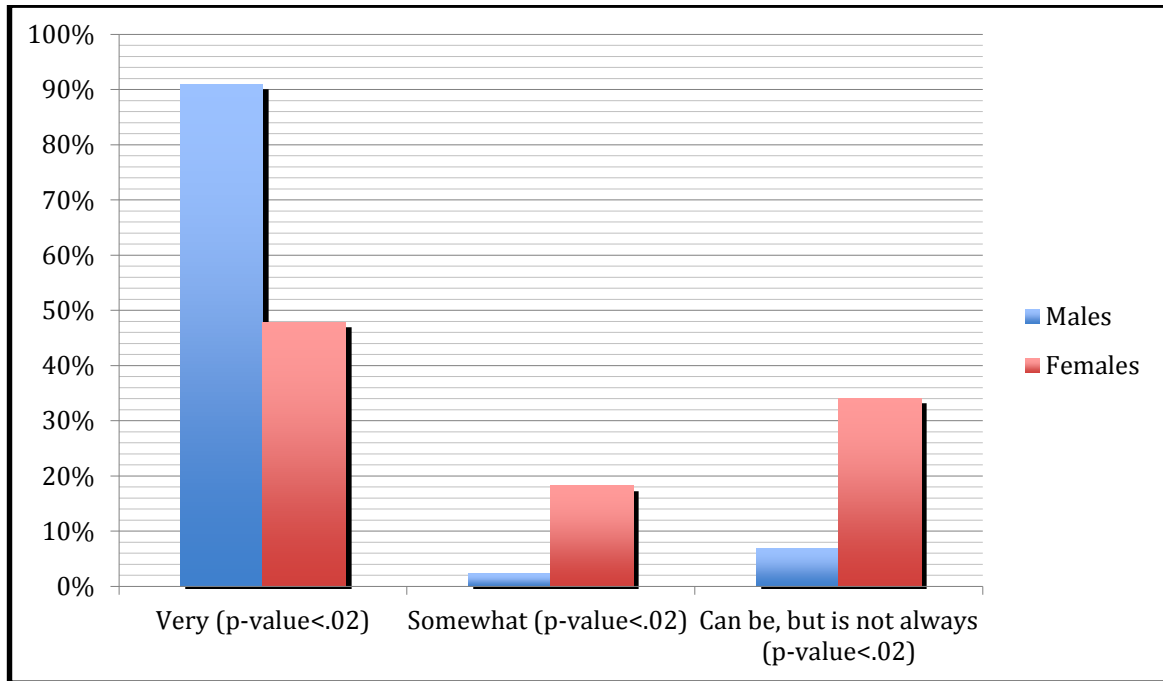


Figure 7. Characterization of perceived severity of Fabry disease for males compared to females

(N=44)

3.2.2 Degree of worry about Fabry disease

Participants were asked to characterize the amount of worry they felt regarding Fabry disease.

Possible responses included:

- I am very worried about Fabry disease
- I am somewhat worried about Fabry disease
- I am worried very little about Fabry disease
- I am not worried about Fabry disease

Approximately 46% of participants indicated they were very worried about Fabry disease, 41% indicated that they were somewhat worried about Fabry disease, 7% indicated they were worried

very little about Fabry disease, and 7% indicated that they were not worried about Fabry disease (Table 7).

Table 7. Characterization of degree of worry about Fabry disease (N=44)

| Degree of worry | Percentage indicated by subjects |
|---------------------|----------------------------------|
| Very worried | 45.5% |
| Somewhat worried | 40.9% |
| Worried very little | 6.8% |
| Not worried | 6.8% |

Participants who indicated they were worried about Fabry disease were asked to describe what worried them the most in a free response format. Of the 41 participants who indicated they had some degree of worry regarding Fabry disease, four participants did not respond to this question. Thematic analysis was performed on the remaining 39 responses to determine themes regarding topics of worry (Table 8).

One of the themes identified was uncertainty. Participants expressed concern regarding the inability to predict the development of symptoms for relatives or for themselves, whether or not their children would inherit Fabry disease, and the availability of treatment and management in the future. One participant described her worry about the future:

Not knowing what my children and I may have to face in the future. Doctors do not know a lot about Fabry. I also worry about Health Coverage in the future.

Another participant writes how she worries about the possibility of passing on Fabry disease to other family members:

I'm worried that I passed this on to my daughter and thus, perhaps, to my 2 grandsons.

A theme of concern for disease impact on children was noted in the responses. Participants expressed worry regarding children's quality of life. One participant discussed her worry regarding her son and his diagnosis of Fabry disease:

I am not worried about my Fabry disease as I have few symptoms. I worry more about my son who is diagnosed with Fabry's disease. It affects him more than me.

Another theme identified was premature death. Participants expressed this worry in regard to their own lifespans and in regard to relatives as well. One participant wrote regarding her own lifespan:

I worry that my life will be cut short. I won't get to do the things I want.

An additional theme identified regarding worry was the inevitability of disease progression. Participants were concerned about the development of more severe symptoms of Fabry disease including renal failure, stroke, and heart disease. A participant explained her concern about the development of more serious disease complications:

Worry about long term symptoms of disease like heart issues or kidney issues

The final theme identified within the responses with regard to worry was cost, specifically regarding disease treatment and management. One participant described cost as her greatest source of worry:

I worry about health care coverage and continuing to pay for treatment.

Table 8. Themes from aspects of Fabry disease most worried about (N=39)

| Themes for analysis | Featured topics |
|---|--|
| Uncertainty | Development of symptoms -For relatives -For self |
| | Inheritance/risk for children |
| | Availability of treatment/management |
| Concern for disease impact on children | Quality of life |
| Premature death | Self |
| | Relatives |
| Disease progression | Resulting burden |
| Cost | Treatment |
| | Management |

3.3 SPECIFIC AIM THREE

3.3.1 Perceived susceptibility

Participants were asked to indicate what symptoms Fabry disease can cause in males and females. Fabry disease symptoms were listed in a table (Table 9). Participants could indicate a symptom caused by Fabry disease by checking a box next to the symptom in question. Participants were then asked to indicate what symptoms of Fabry disease they had and what symptoms they thought they were likely to develop in two separate tables. These responses were combined for analysis to represent symptoms participants' had and/or felt they were likely to develop. Questions were

intended to characterize the perceived susceptibility of males with Fabry disease, females with Fabry disease, and participants' perceived personal susceptibility to Fabry disease symptoms (Table 10).

Table 9. Symptoms of Fabry disease

| | |
|--|--|
| Proteinuria (excess protein in the urine) | Kidney failure |
| Congestive heart failure (heart cannot pump enough blood to meet the body's needs) | Heart attack |
| Enlargement of heart | Abnormal heart rhythm (irregular heart beat) |
| Stroke | Transient ischemic attack (mini-stroke) |
| Chronic pain | Burning/numbness/tingling in hands or feet |
| Heat and/or cold intolerance | Problems with sweating |
| Abdominal pain | Diarrhea and/or constipation |
| Angiokeratomas (clustered red skin markings) | Corneal whorls (pattern on transparent area of eye only visible by slit lamp exam) |
| Pulmonary (lung) disease | Depression and/or anxiety |

Table 10. Means of characterization of Fabry disease susceptibility for males, females, and participants

| Question | Intent to characterize |
|--|--|
| Based on your understanding, what symptoms can Fabry disease cause in males? | Susceptibility of males to Fabry disease symptoms |
| Based on your understanding, what symptoms can Fabry disease cause in females? | Susceptibility of females to Fabry disease symptoms |
| What symptoms of Fabry disease, if any, do you have? | Participant-susceptibility to Fabry disease symptoms |
| What symptoms of Fabry disease, if any, do you feel you are likely to develop? | |

In males, the percentage of symptoms participants indicated that could be caused by Fabry disease (male susceptibility) were as follows: proteinuria (91%), congestive heart failure (66%), enlargement of heart (68%), stroke (89%), chronic pain (95%), heat/cold intolerance (98%), abdominal pain (86%), angiokeratomas (100%), pulmonary disease (50%), kidney failure (95%), heart attack (80%), abnormal heart rhythm (73%), TIA (80%), burning/numbness/tingling

(100%), problems with sweating (93%), diarrhea/constipation (93%), corneal whorls (93%), and depression/anxiety (89%) (Table 11).

In females, the percentage of symptoms participants' indicated that could be caused by Fabry disease (female susceptibility) were as follows: proteinuria (91%), congestive heart failure (64%), enlargement of heart (64%), stroke (84%), chronic pain (86%), heat/cold intolerance (91%), abdominal pain (89%), angiokeratomas (89%), pulmonary disease (43%), kidney failure (86%), heart attack (77%), abnormal heart rhythm (77%), TIA (77%), burning/numbness/tingling (96%), problems with sweating (91%), diarrhea/constipation (91%), corneal whorls (96%), and depression/anxiety (86%) (Table 11).

The percentage of symptoms participants' indicated that they had and/or were likely to develop (personal susceptibility) were as follows: proteinuria (64%), congestive heart failure (21%), enlargement of heart (23%), stroke (37%), chronic pain (43%), heat/cold intolerance (71%), abdominal pain (39%), angiokeratomas (50%), pulmonary disease (19%), kidney failure (43%), heart attack (39%), abnormal heart rhythm (52%), TIA (39%), burning/numbness/tingling (75%), problems with sweating (43%), diarrhea/constipation (59%), corneal whorls (68%), and depression/anxiety (50%) (Table 11).

Analysis using McNemar's test of homogeneity was performed in order to characterize the perceived susceptibility of females with Fabry disease compared to the perceived personal susceptibility of participants. The p-value for this analysis was adjusted using the Bonferroni correction to a value of 0.003. Statistical significance was observed for symptoms of Fabry disease including proteinuria, congestive heart failure, enlargement of heart, stroke, chronic pain, heat/cold intolerance, abdominal pain, angiokeratomas, pulmonary disease, kidney failure, heart attack, abnormal heart rhythm, TIA, burning/numbness/tingling, problems with sweating,

diarrhea/constipation, corneal whorls, and depression/anxiety (Table 13 and Figure 9). A trend was found regarding susceptibility to the following symptoms: heat/cold intolerance (p-value of 0.0268), pulmonary disease (p-value of 0.0098), abnormal heart rhythm (p-value of 0.0162), burning/numbness/tingling (p-value of 0.0133), and diarrhea/constipation (p-value of 0.0059). However, using the adjusted p-value of 0.003 these analyses were determined to be statistically insignificant. All of the symptoms, regardless of statistical significance, were selected with greater frequency for females with Fabry disease than for the participants' personally (Table 12).

Table 11. Percentage of symptoms caused by Fabry disease for males, females and for participants personally

(N=44)

| Symptoms | Males | Females | Participants |
|----------------------------------|--------------|----------------|---------------------|
| Proteinuria | 90.91% | 90.91% | 63.64% |
| Congestive heart failure | 65.91% | 63.64% | 20.45% |
| Enlargement of heart | 68.18% | 63.64% | 22.73% |
| Stroke | 88.64% | 84.09% | 38.64% |
| Chronic pain | 95.45% | 86.36% | 43.18% |
| Heat/cold intolerance | 97.73% | 90.91% | 70.45% |
| Abdominal pain | 86.36% | 88.64% | 38.64% |
| Angiokeratomas | 100.00% | 88.64% | 50.00% |
| Pulmonary disease | 50.00% | 43.18% | 18.18% |
| Kidney failure | 95.45% | 86.36% | 43.18% |
| Heart attack | 79.55% | 77.27% | 38.64% |
| Abnormal heart rhythm | 72.73% | 77.27% | 52.27% |
| TIA | 79.55% | 77.27% | 38.64% |
| Burning/numbness/tingling | 100.00% | 95.45% | 75.00% |
| Problems with sweating | 93.18% | 90.91% | 43.18% |
| Diarrhea/constipation | 93.18% | 90.91% | 59.09% |
| Corneal whorls | 93.18% | 95.45% | 68.18% |
| Depression/anxiety | 88.64% | 86.36% | 50.00% |

Table 12. McNemar's test of homogeneity analysis of perceived susceptibility of females with Fabry disease compared to perceived personal susceptibility of participants (N=44)

| Symptoms | Females | Personal | McNemar's chi-squared | Degrees of freedom | p-value |
|---|---------|----------|-----------------------|--------------------|-----------------------|
| Proteinuria | 90.91% | 63.64% | 10.0833 | 1 | 0.0015* |
| Congestive heart failure | 63.64% | 20.45% | 17.0526 | 1 | 3.64E ⁻⁵ * |
| Enlargement of heart | 63.64% | 22.73% | 15.0588 | 1 | 0.0001* |
| Stroke | 84.09% | 38.64% | 17.0526 | 1 | 3.64E ⁻⁵ * |
| Chronic pain | 86.36% | 43.18% | 16.0556 | 1 | 6.15E ⁻⁵ * |
| Heat/cold intolerance | 90.91% | 70.45% | 4.9 | 1 | 0.0269 |
| Abdominal pain | 88.64% | 38.64% | 19.0476 | 1 | 1.28E ⁻⁵ * |
| Angiokeratomas | 88.64% | 50.00% | 13.4737 | 1 | 0.0002* |
| Pulmonary disease | 43.18% | 18.18% | 6.6667 | 1 | 0.0098 |
| Kidney failure | 86.36% | 43.18% | 15.4286 | 1 | 8.57E ⁻⁵ * |
| Heart attack | 77.27% | 38.64% | 15.0588 | 1 | 0.0001* |
| Abnormal heart rhythm | 77.27% | 52.27% | 5.7857 | 1 | 0.0162 |
| TIA | 77.27% | 38.64% | 13.4737 | 1 | 0.0002* |
| Burning/numbness/tingling | 95.45% | 75.00% | 6.125 | 1 | 0.0133 |
| Problems with sweating | 90.91% | 43.18% | 18.05 | 1 | 2.15E ⁻⁵ * |
| Diarrhea/constipation | 90.91% | 59.09% | 7.5789 | 1 | 0.0059 |
| Corneal whorls | 95.45% | 68.18% | 10.0833 | 1 | 0.0015* |
| Depression/anxiety | 86.36% | 50.00% | 12.5 | 1 | 0.0004* |
| *p-value<0.003 is statistically significant | | | | | |

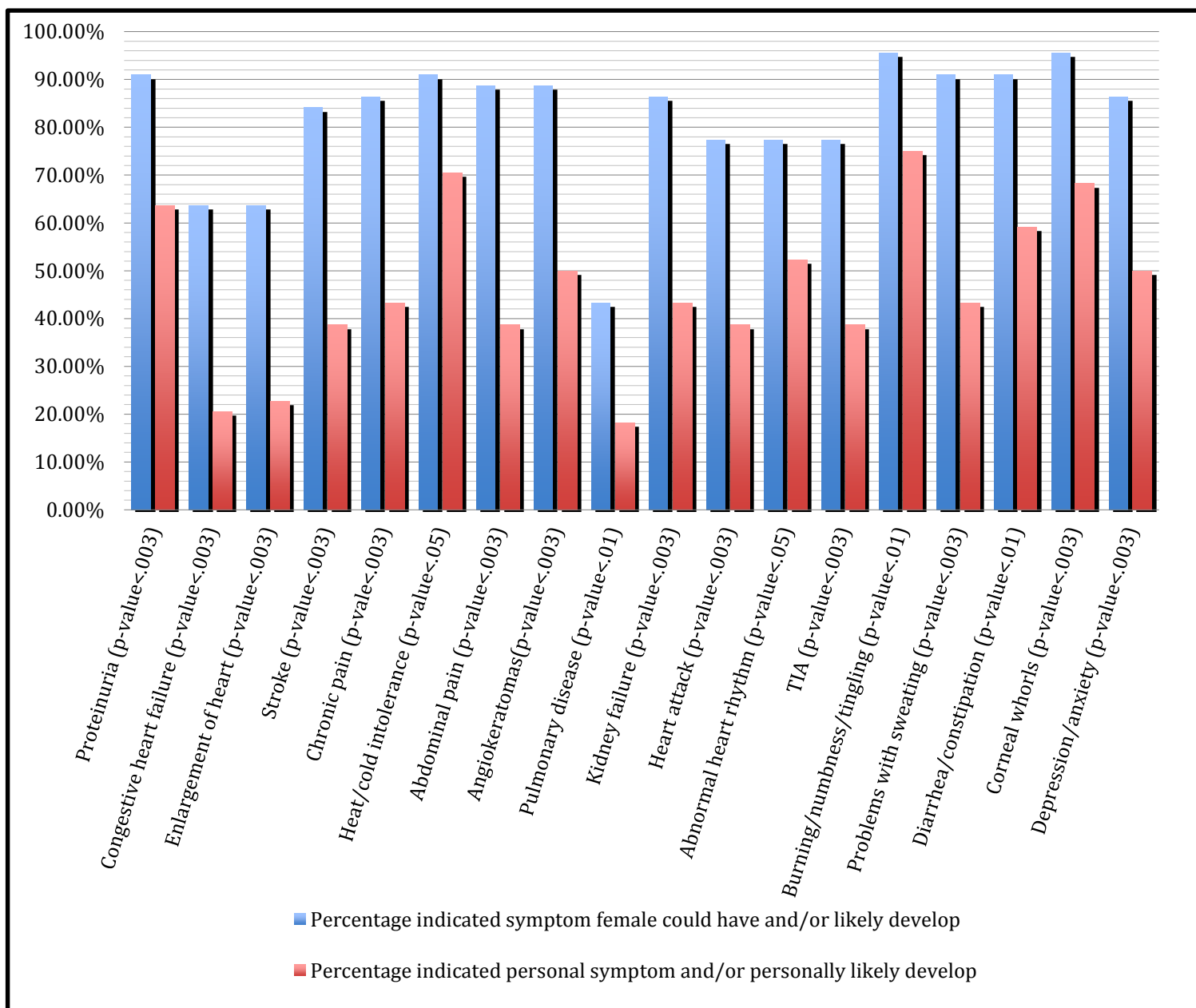


Figure 8. Perceived susceptibility of females to Fabry disease symptoms compared to perceived personal susceptibility (N=44)

3.3.2 Assessment of “carrier” terminology

In an attempt to characterize the usage and perceived appropriateness of the term “carrier” in regard to females diagnosed with Fabry disease, participants were asked the following questions in a yes or not format:

- Have you ever used the word “carrier” to describe yourself?
- Have any of your physicians or health care providers used the word “carrier” to describe your diagnosis?
- Do you think this term is appropriate?

The term “carrier” was not defined for participants. Approximately 66% of participants have used the word “carrier” to describe themselves. Of note, four of the 29 participants who indicated they have used the term “carrier” to describe themselves justified this response by explaining they had only used the term in the past or currently try not to use the term. These justifications were not asked for, but were written in the margins of the questionnaires. Approximately 77% of participants indicated that a physician or healthcare provider had described them as a “carrier”. One participant marked both “yes” and “no” in her response to the question “Do you think this term is appropriate”. Her response was not used in the analysis of the perceived appropriateness of the term “carrier”. Of the 43 remaining participants, approximately 40% of participants indicated they believed the term “carrier” was appropriate (Figure 10).

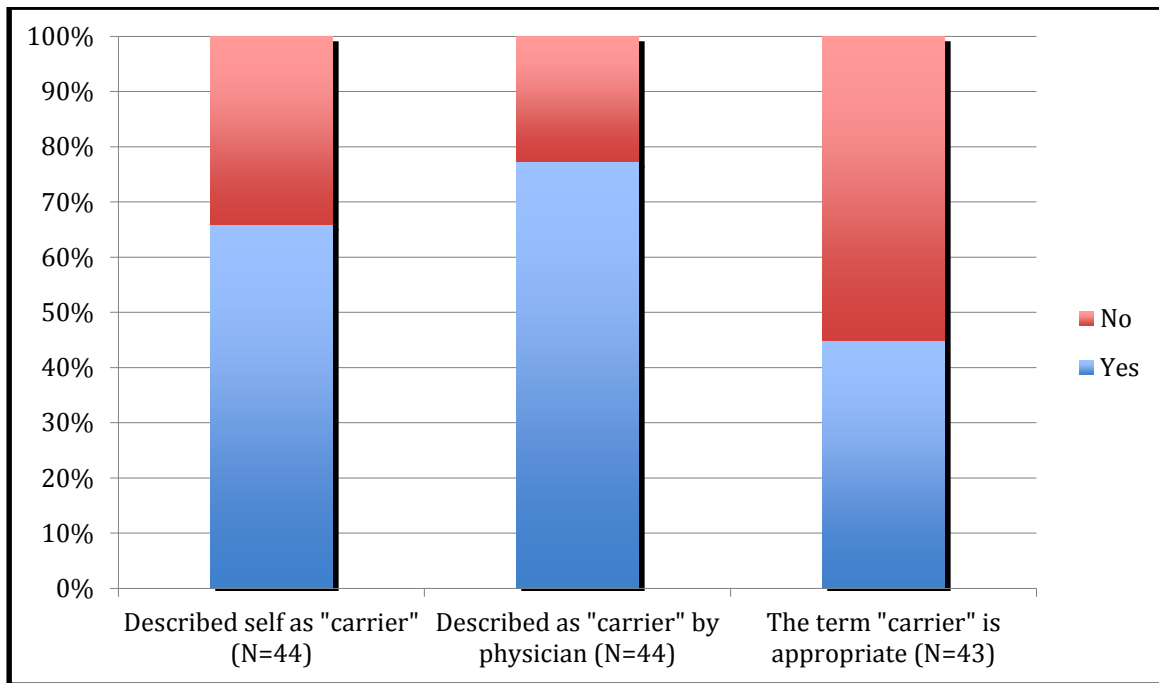


Figure 9. Usage and perceived appropriateness of the term “carrier”

Participants were asked to explain why they believed the term “carrier” was either appropriate or inappropriate in a free response format. Thematic analysis was used to determine common themes among participants who thought the term “carrier” was appropriate and among participants who thought the term “carrier” was inappropriate (Table 13).

Of the 17 participants that indicated they believed that the term “carrier” was an appropriate description of themselves, one participant did not describe why she thought the term carrier was appropriate. Thematic analysis was completed on the remaining 16 participants’ responses. Overall, participants felt that the term “carrier” indicated the capability to pass the disease on, regardless of whether or not the participants had disease symptoms. One participant who described the term “carrier” as appropriate wrote:

I have symptoms but I also “carry” it/pass it on.

Of the 26 participants that indicated they did not believe the term “carrier” was an appropriate description of themselves, two participants did not describe why they thought the term was inappropriate. Thematic analysis was completed on the remaining 24 participants’ responses. In general, participants felt the term “carrier” diminished the amount and/or severity of symptoms of Fabry disease a female can have. A participant who described the term as inappropriate wrote:

Women can experience the same symptoms and be as severely affected

Table 13. Themes from participants who identify the term “carrier” as appropriate and inappropriate

| | Percent of participants | Theme |
|----------------------|-------------------------|--|
| Appropriate | 40% (N=44) | Ability to pass on disease, regardless of symptoms (N=17) |
| Inappropriate | 60% (N=44) | Diminishment of amount /severity of symptoms a female can have (N=24) |

3.4 SPECIFIC AIM FOUR

3.4.1 Perceived benefits of treatment, evaluation and monitoring

Participants were asked if they were currently receiving ERT in the treatment of their Fabry disease. Approximately 57% of participants were currently taking ERT (Figure 11). Participants currently on ERT (25 total) were then asked to describe in an open-ended question what their expectations of ERT were and how ERT did or did not meet their expectations. Of the 25

participants who were on ERT, 24 provided responses regarding their expectations of ERT. Expectations of ERT provided by participants included: improve symptoms (specifically gastrointestinal, pain, acroparasthesias, proteinuria, and sweating), prolong life, prevent symptoms (specifically organ damage and stroke), stabilize symptoms (specifically renal and cardiac), enhance energy, feel better, and lose weight. One participant indicated she did not have expectations for ERT (Table 14). It was not possible to discern whether the expectations listed by the aforementioned 24 participants were met using the responses provided by participants in the open-ended question, as not all responses were relevant to the specific question asked. However, it was possible to determine if participants had a positive or negative experience with ERT from the responses using thematic analysis. These categorizations were designated in an attempt to categorize participant satisfaction with ERT. Analysis was based on participant word choice. For example, participants' found to have a positive experience used words that were positive in nature when describing their experience with ERT such as "improved", "better", "exceeded", and "helped". Participants' found to have a negative experience used words that were negative in nature when describing their experience with ERT such as "no", "cannot", "sick", "worse", and "frustrating". Approximately 49% of participants on ERT had a positive experience and 37% of participants on ERT had a negative experience (Figure 12). About 14% of participants currently receiving ERT did not fit into either the positive or negative category based on their language used in description of their experience with ERT. These participants used the phrase "not sure" or used a combination of words that were both positive and negative in nature when describing ERT, suggesting that they were grappling with their experience with ERT.

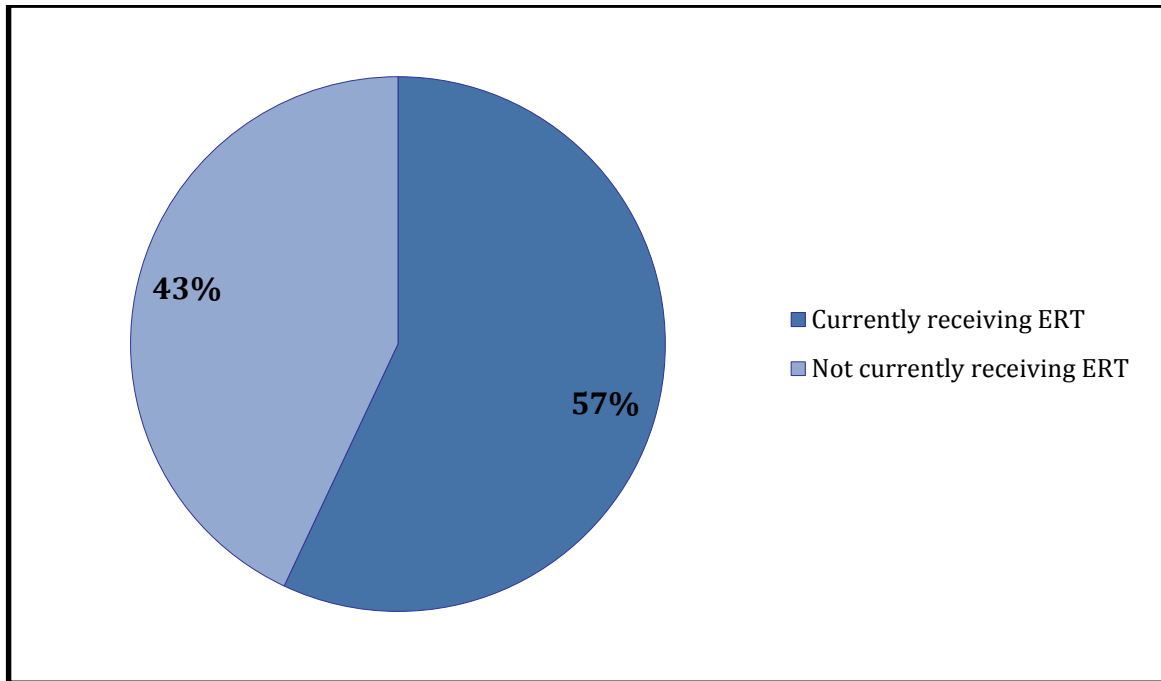


Figure 10. Percentage of participants currently receiving ERT

Table 14. Expectations of ERT

| | |
|------------------|--------------------|
| Improve symptoms | Prevent symptoms |
| Prolong life | Stabilize symptoms |
| Feel better | More energy |
| Lose weight | None |

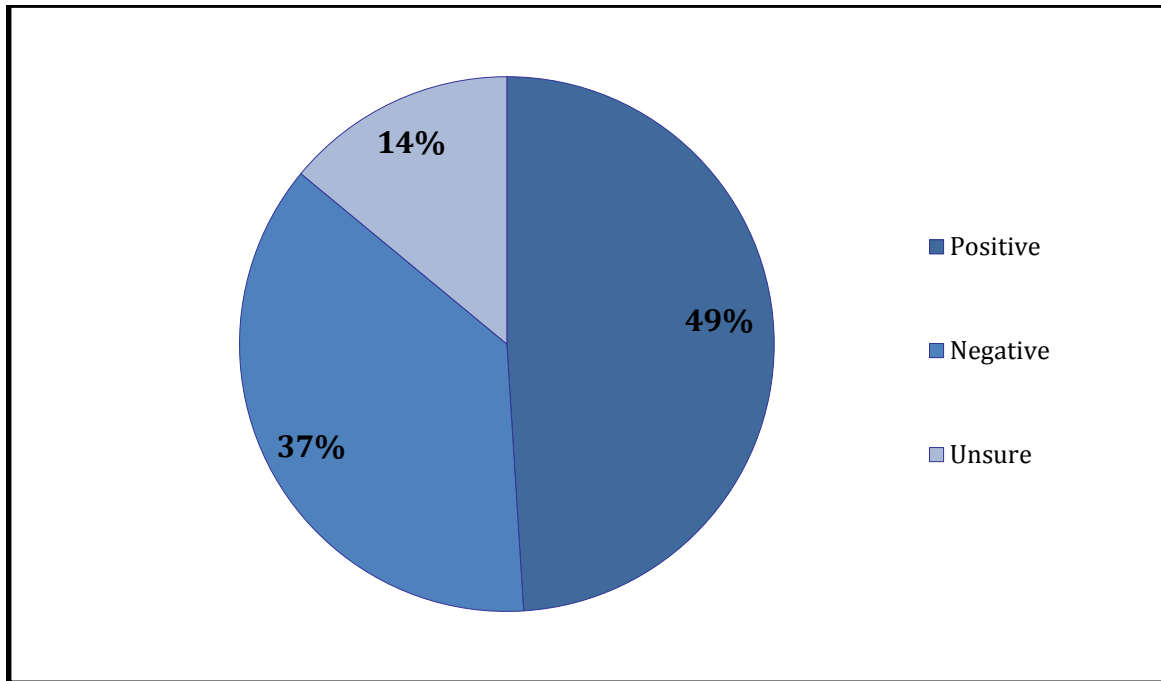


Figure 11. Characterization of experience with ERT (N=24)

3.5 SPECIFIC AIM FIVE

3.5.1 Perceived barriers to treatment, evaluation and monitoring

A table of potential barriers to evaluation and monitoring was provided to participants within the questionnaire. Participants were asked to mark what barriers, if any, prevented them from participating in monitoring and evaluations. Participants were also asked in an open-ended question to elaborate on barriers they marked in the table or to list additional barriers not provided. Approximately 64% participants indicated they felt at least one barrier to evaluation either provided in the table or written in the open-ended question section (Figure 13). Of the barriers provided in the questionnaire, the most common barrier indicated was costs not covered by

insurance (36%), followed by distance from centers (30%), and anxiety (25%) (Table 15). Barriers listed by participants that were not included in the provided table included: age (this was not further specified by participants), apathy, denial, avoidance of perceived pressure for ERT, and additional unrelated to Fabry disease health concerns (i.e. family history of dementia) (Table 16). Participants elaborated about costs not covered by insurance. Participants described that the costs of non-ERT prescriptions, copays, high deductibles, and examinations and evaluations not covered by insurance prevented them from completing recommended evaluations (Table 17).

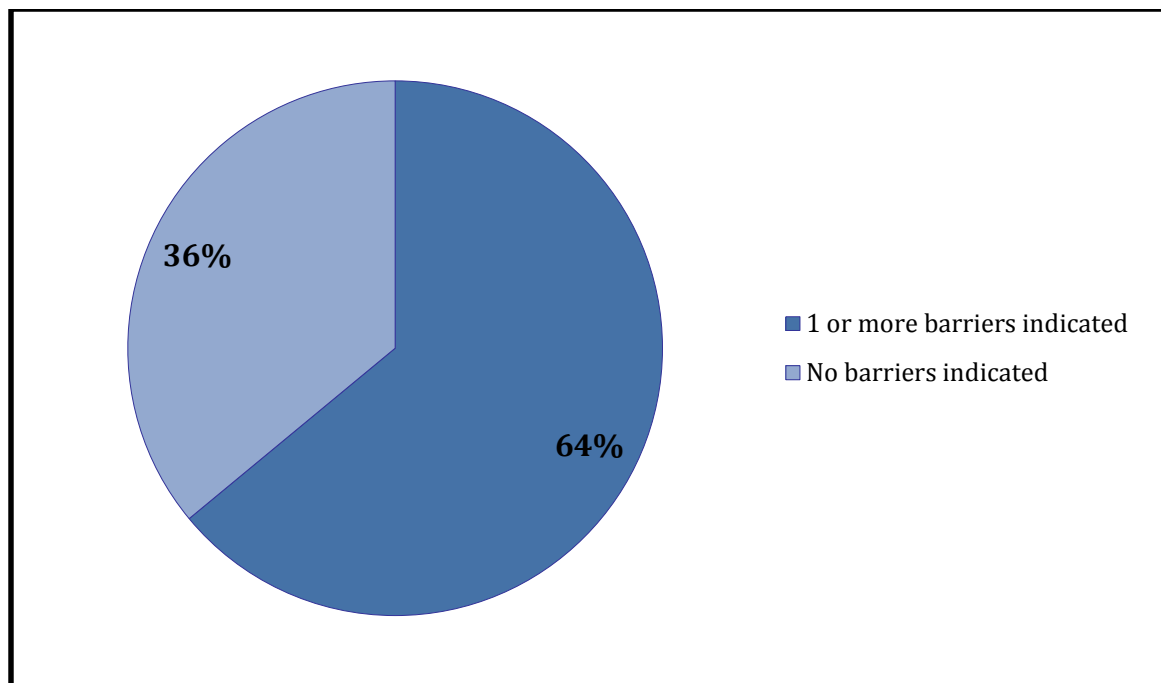


Figure 12. Percentage of participants with and without barriers to evaluations and monitoring

Table 15. Barriers to treatment, evaluation and monitoring (N=44)

| Barriers | Percentage indicated by participants |
|---|---|
| Costs not covered by insurance | 36.36% |
| Distance from centers | 29.55% |
| Anxiety | 25.00% |
| Feeling overwhelmed | 20.45% |
| Desire to keep focus on more severely affected family | 18.18% |
| Symptoms not severe | 15.91% |
| Frustration with amount of recommended tests | 15.91% |
| Time | 15.91% |
| Frustration with lack of provider knowledge | 13.64% |
| Care of family member affected with Fabry disease | 13.64% |
| Worry | 11.36% |
| Difficulties obtaining transportation | 11.36% |
| Fear of testing | 9.09% |
| Depression | 9.09% |
| Insurance/work discrimination | 9.09% |
| Lack of insurance | 9.09% |
| Job responsibilities | 6.82% |
| Childcare responsibilities | 6.82% |
| Sadness | 6.82% |
| Lack of support/encouragement | 6.82% |
| Anger about diagnosis | 6.82% |
| Poor Health | 6.82% |
| Not enough info | 4.55% |
| Feeling undeserving of care/attention | 2.27% |
| Concern about test results | 2.27% |
| Guilt | 2.27% |

Table 16. Additional barriers listed by participants

| |
|--|
| Age |
| Apathy |
| Denial |
| Perceived pressure for ERT |
| Additional, unrelated to Fabry disease health concerns |

Table 17. Costs not covered by insurance described by participants

| | |
|--------------------------------|------------------------------|
| Prescriptions unrelated to ERT | Copays |
| High deductibles | Examinations and evaluations |

3.6 SPECIFIC AIM SIX

3.6.1 Modifying variables and cues to action: completion of recommended evaluations

Participants were asked to indicate what evaluations had been recommended to them throughout the care of their Fabry disease. Evaluations were listed in a table (Table 18). Participants could indicate an evaluation had been recommended to them by checking a box next to the evaluation in question. One participant did not respond consistently across questions regarding evaluations so her responses were excluded from analysis, leaving a total of 43 participants for analysis. In the care of their Fabry disease, the percentage of evaluations recommended to participants were as follows: electrocardiogram (95%), echocardiogram (93%), brain MRI (86%), lipid panel (86%), 24-hour urine test (81%), GL3 testing (81%), Fabrazyme antibody (65%), heart MRI (49%), slit lamp eye exam (49%), audiologic evaluation (44%), 24-hour holter monitor (42%), pulmonary function test (33%), and kidney biopsy (19%) (Table 19).

Participants were also asked to indicate which evaluations they had completed at diagnosis and which evaluations they continued to perform on a regular basis using the table format described above. The percentage of recommended evaluations that were completed at the time of diagnosis and on a regular basis were calculated. Only participants who had been recommended a certain test were included in these calculations. Of the 35 participants who were recommended

to have a 24-hour urine test, 74% had the evaluation done at their time of diagnosis and 57% have the evaluation done regularly. Of the 41 participants who were recommended to have an electrocardiogram, 63% had the evaluation done at their time of diagnosis and 68% have the evaluation done regularly. Of the 18 participants who were recommended to have a 24-hour holter monitor, 39% had the evaluation done at their time of diagnosis and 33% have the evaluation done regularly. Of the 19 participants who were recommended to have an audiologic evaluation, 58% had the evaluation done at their time of diagnosis and 26% have the evaluation done regularly. Of the 37 participants who were recommended to have a brain MRI, 65% had the evaluation done at their time of diagnosis and 32% have the evaluation done regularly. Of the 28 participants who were recommended to have a Fabrazyme antibody, 57% had the evaluation done at their time of diagnosis and 46% have the evaluation done regularly. Of the 37 participants who were recommended to have a lipid panel, 65% had the evaluation done at their time of diagnosis and 89% have the evaluation done regularly. Of the 8 participants who were recommended to have a kidney biopsy, 63% had the evaluation done at their time of diagnosis and 25% have the evaluation done regularly. Of the 40 participants who were recommended to have an echocardiogram, 70% had the evaluation done at their time of diagnosis and 73% have the evaluation done regularly. Of the 21 participants who were recommended to have a heart MRI, 52% had the evaluation done at their time of diagnosis and 33% have the evaluation done regularly. Of the 14 participants who were recommended to have a pulmonary function test, 50% had the evaluation done at their time of diagnosis and 50% have the evaluation done regularly. Of the 21 participants who were recommended to have a slit lamp eye exam, 62% had the evaluation done at their time of diagnosis and 38% have the evaluation done regularly. Of the 35 participants who were recommended to

have a GL3 testing, 77% had the evaluation done at their time of diagnosis and 51% have the evaluation done regularly (Figure 14).

In order to calculate whether a recommended evaluation had been completed at any time in the care of a participant's Fabry disease, responses from evaluations completed at the time of diagnosis and evaluations that were completed on a regular basis were combined to represent a binary response system (completed at any point in time and never completed). McNemar's test of homogeneity was used to determine if there was a statistically significant difference between the proportions of participants that were recommended to undergo an evaluation compared to the proportion of patients who completed the evaluation. The p-value for this analysis was adjusted using the Bonferroni correction to a value of 0.004. Individual p-values for each evaluation were corrected for one-sided analysis. A trend was found for the completion of the following recommended evaluations: 24-hour holter monitor (p-value of 0.0079), brain MRI (p-value of 0.0067), Fabrazyme antibody (p-value of 0.0228), and heart MRI (p-value of 0.0352). However, using the adjusted p-value of 0.004 these analyses were determined to be statistically insignificant. Of note, for these evaluations a higher number of evaluations were recommended to participants than were completed (Table 20).

Table 18. Evaluations for Fabry disease

| | |
|--|---|
| 24 hour urine test (test for kidney function) | Renal (kidney) biopsy |
| Electrocardiogram/EKG (records heart's electrical activity using electrodes) | Echocardiogram (ultrasound of the heart) |
| 24 hour holter heart monitoring (cardiac event monitoring) | Heart MRI (uses magnets to create a picture of the heart) |
| Audiologic (hearing) evaluation | Pulmonary (lung) function test (breathing test) |
| Brain MRI (uses magnets to create a picture of the brain) | Slit Lamp eye exam |
| Fabrazyme antibody testing (blood test) | GL-3 testing (blood or urine test) |
| Lipid panel (cholesterol blood test) | |

Table 19. Percentage of evaluations recommended to participants (N=43)

| Evaluation | Percentage recommended to participants |
|-------------------------|--|
| Electrocardiogram | 95.35% |
| Echocardiogram | 93.02% |
| Brain MRI | 86.05% |
| Lipid panel | 86.05% |
| 24 hour urine test | 81.40% |
| GL-3 testing | 81.40% |
| Fabrazyme antibody | 65.12% |
| Heart MRI | 48.84% |
| Slit lamp exam | 48.84% |
| Audiologic evaluation | 44.19% |
| 24 hour holter monitor | 41.86% |
| Pulmonary function test | 32.56% |
| Kidney biopsy | 18.60% |

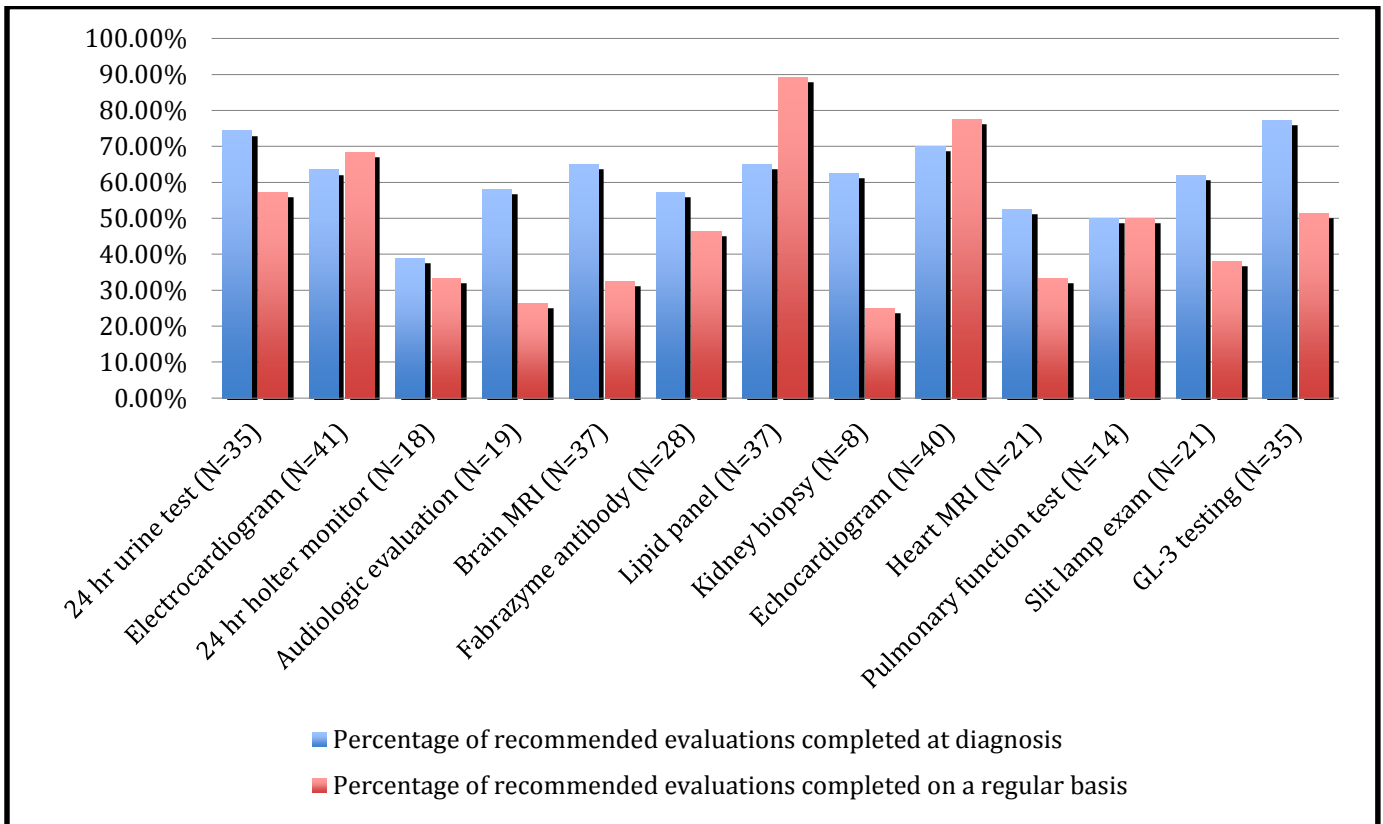


Figure 13. Comparison of completion of recommended evaluations at time of diagnosis and continued on a regular basis

Table 20. McNemar's test of homogeneity analysis for completion of recommended evaluations

| Evaluation | Number of participants indicated evaluation recommended (N) | Percent of evaluations completed at any time | McNemar's chi-squared | Degrees of freedom | p-value |
|---|--|---|------------------------------|---------------------------|----------------|
| 24-hour holter monitor | 18 | 50% | 5.8182 | 1 | 0.0079 |
| Brain MRI | 37 | 76% | 6.125 | 1 | 0.0067 |
| Fabrazyme antibody | 28 | 75% | 4 | 1 | 0.0228 |
| Heart MRI | 21 | 62% | 1.4545 | 1 | 0.0352 |
| *p-value<0.004 is statistically significant | | | | | |

(a) Impact of perceived severity and worry

Regression analysis was performed to determine if perceived severity or worry impacted the completion of recommended evaluations. Only participants who reported a given recommended evaluation were included in analysis. The p-value for this analysis was adjusted using the Bonferroni correction to a value of 0.004. Analyses failed to identify a statistically significant relationship between perceived severity or worry and completion of recommended evaluations.

(b) Impact of perceived susceptibility

Analysis using Fisher's exact test was performed to determine if perceived personal susceptibility to Fabry disease symptoms impacted the completion of recommended evaluations. Only participants who reported a given recommended evaluation were included in analysis. Perceived susceptibility for each Fabry disease symptom (18 total symptoms) was compared to completion of each evaluation recommended to a participant (13 total evaluations) and assessed for statistical significance (234 combinations). The p-value for this analysis was adjusted using the Bonferroni

correction to a value of 0.0002. Analyses failed to identify a relationship of statistical significance between perceived susceptibility and completion of recommended evaluations.

Analysis using Fisher's exact test was also performed to determine if the presence of specific symptoms at the time of diagnosis affected the completion of recommended evaluations. The adjusted p-value of 0.0002 described above was used in this analysis. Analyses failed to identify a statistically significant association between specific symptoms at diagnosis and completion of recommended evaluations.

3.6.2 Modifying variables: impact of a diagnosis of Fabry disease

All participants (100%) reported a diagnosis of Fabry disease. A diagnosis of Fabry disease was defined as "by genetic testing or family history alone".

3.6.2.1 Characterization of feelings about and reactions to diagnosis

Participants were asked in an open-ended question to explain how they felt after receiving a diagnosis of Fabry disease (Table 21 for list of themes identified within responses). The theme of concern for children and other relatives was identified within the responses. Emotions connected to the theme of concern for children included sadness, depression/hopelessness, and fear. One participant wrote with regard to her diagnosis:

It was sad that I might have passed this on to my children

Another participant expressed fear for her children to inherit Fabry disease:

Fear I had passed it to one of my three children

While most of the responses eluded to feelings of guilt regarding their children's inheritance of Fabry disease, only one participant self-identified the feeling of guilt associated with her diagnosis.

Guilty. The mutation started with me and I passed it on to my daughter. She was diagnosed first. Then I was found to have it.

The theme of concern for self was also identified in the responses. These responses were permeated with a sense of foreboding or dread, sadness, and fear. A participant expressed feelings of excessive sadness and worry with regard to her diagnosis:

Very depressed and stressed. Saw what my dad went through and died young- 52 yrs old.

Another theme identified in the responses was validation. Participants expressed a sense of relief in learning that their symptoms were not imagined or for finding an explanation for their symptoms. One participant wrote:

Understood what was causing the symptoms that I always had. (Like not sweating.)

Additionally, participants appreciated finding the explanation for their relatives' unexplained symptoms or deaths. A participant expressed a sense of relief that she had learned the reason that her father passed away:

Relieved to finally know what killed my father in 1964 and relieved to be treated before its too late in my case.

Overall, the themes of validation, concern for children and other relatives, and concern for self were often expressed simultaneously. An example of a response with a combination of the themes of validation and concern for self is shown below:

Relieved I wasn't "making up" and going crazy with symptoms that began when I was 16 years old. It also put me in a depressed state knowing what would happen to me medically. Seeing my mom being sick and dying with the Fabry was a major reality check.

Another participant expressed the themes of concern for self and concern for children and other relatives when she wrote:

It was very upsetting. I was afraid for my own health and the health of any children I might have.

Finally, a theme of indifference and/or delayed reaction was identified within the responses of ten participants. These participants elaborated regarding the sources of their indifference. Explanations for indifference included: young age at diagnosis (either led to a normalization of Fabry disease or inability to understand implications), labeled as a carrier (misunderstanding that not at risk for disease complications), and an assumption of diagnosis (expected a diagnosis of Fabry disease prior to diagnosis). One participant explained her perspective:

My diagnosis came when I was only 14 y/o. At that time, "only a carrier" was used to describe me. Therefore, I didn't give it much thought until older- even though I was symptomatic.

Another participant demonstrated her indifference due to her assumed diagnosis:

Already knew I had it. 0 change (Δ).

Another participant explained the normalization of diagnosis for both her and her sister, attributing this phenomenon to the age of diagnosis:

I was 5, this has always been a part of my life. For me this is my normal, my sister was born a year after we found out so she has known all her life.

Another participant explained how the age of her diagnosis impacted her reaction:

I was young (11 years old) and remember being indifferent/not fully understanding. It wasn't until I became an adult, responsible for my own health decisions that I realized the seriousness.

Table 21. Themes from feelings and reactions to diagnosis (N=44)

| Themes from analysis | Contributing emotions |
|---|--|
| Concern for children and other relatives | Excessive sadness |
| | Fear |
| | Guilt |
| Concern for self | Dread/sense of foreboding |
| | Excessive sadness |
| | Fear |
| Validation | Relief |
| Indifference and/or delayed reaction | Diagnosis at young age |
| | -Normalization |
| | -Inability to comprehend implications |
| | Labeled as “carrier” |
| | -Believed not at-risk for disease symptoms |
| | Assumed/expected diagnosis |

In addition to these themes, emotions including anger, hyperawareness of symptoms and surprise were described.

3.6.2.2 Impact of diagnosis on ideas about health

Approximately 75% of participants indicated that a diagnosis of Fabry disease impacted their ideas about their health (Figure 15).

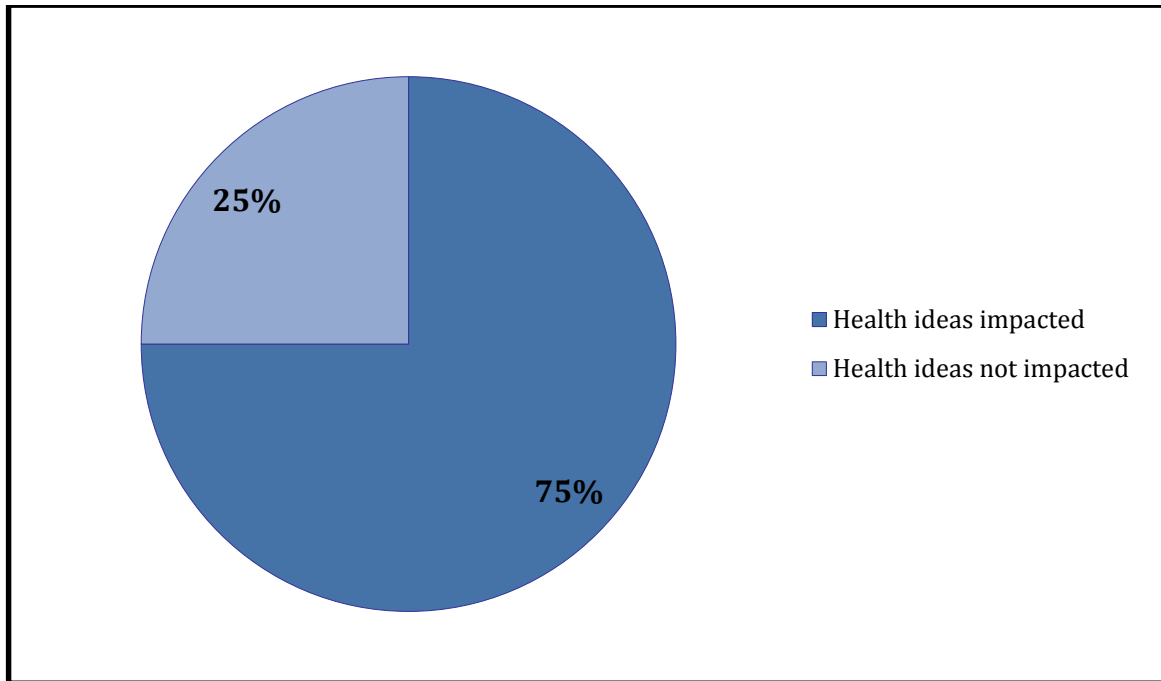


Figure 14. Proportion of participants with health ideas impacted by diagnosis of Fabry disease
(N=44)

Participants who indicated a change in health beliefs were asked to explain how their ideas about their health were impacted in an open-ended question. Of the 33 participants who indicated that a diagnosis of Fabry disease impacted their health beliefs, five participants did not complete the question and two participants provided responses that did not expand or explain how a diagnosis of Fabry disease impacted their ideas about their health. Thematic analysis was utilized to identify patterns or themes in the 26 remaining responses (Table 22).

A theme identified from the responses was hyperawareness of disease symptoms and general health issues. Participants expressed an overall increased sensitivity to health issues and Fabry disease symptoms. A participant explained how her diagnosis of Fabry disease increased her awareness of her health:

More aware if I would have any changes in my health.

Another theme identified was a change in health care practices. Changes in health care practices varied from basic changes like improved diet or increased exercise to more extreme measures such as pregnancy risk management by tubal ligation. Participants also discussed how the introduction of Fabry disease treatment into their regimen resulted in a change in health beliefs. One participant described a change in her health practices:

I try to eat healthier now. Try to rest more. I do worry about my future now.

One participant described her reproductive decisions due to her diagnosis of Fabry disease:

Tubal ligation at 21 years old to not take a chance of giving to a child.

Additionally, a theme expressed by participants was a change in perception of health. Changes in perception included shortened lifespan, reduced quality of life and health, as well as an improved understanding of their own health. A participant expressed how her diagnosis affected her self-perception of health.

I felt like my lifespan was automatically shortened and quality of life reduced.

Participants also described how learning about Fabry disease improved their understanding of their symptoms or family history. One participant demonstrated how her diagnosis improved her understanding of her health:

I know I became aware of a whole new world and new vocabulary. But with the developing health problems it made sense of what was happening.

Finally, a theme of increased worry was identified in responses. Increased worry was associated with health insurance and work discrimination, long-term issues, and deterioration of health. One comment written by a participant suggested that she was concerned regarding her insurance coverage:

There are not many alternative medical treatments to relieve symptoms or long term prognosis. Ability to be insured.

Another participant described increased worry about long-term health issues:

Felt like something else medical I had to deal with. Worried about long term issues.

A participant described increased worry about her health:

I became very concerned about my kidney function. My father died from renal failure.

Many of the themes identified were expressed simultaneously in participants' responses. This phenomenon can be seen in some of the quotes selected above. In another example, one response demonstrated the themes of change in perception of health, increased worry, and change in health care practices.

The symptoms I have were easy to ignore before. Now I know they may be a sign of more serious problems, so I am much more worried than before. I keep thinking, that I have to take really good care of my self.

Table 22. Impact of diagnosis on health beliefs (N=26)

| Themes from analysis | Components of themes |
|-----------------------|-------------------------|
| Hyperawareness | Fabry disease symptoms |
| | General health concerns |
| | Improved diet |
| | Increased exercise |

Table 22 Continued

| | |
|--|------------------------------------|
| Change in health care practices | Treatment for Fabry disease |
| | Pregnancy prevention |
| Change in perception of health | Shortened lifespan |
| | Reduced quality of life and health |
| | Better understanding of health |
| Increased worry | Insurance/Work discrimination |
| | Long-term issues |
| | Deterioration of health |

3.6.3 Modifying variables: participants currently receiving ERT compared to participants not currently receiving ERT

Analyses were performed to identify differences in demographics, perceived severity, perceived susceptibility, perceived barriers to treatment evaluation and monitoring, and completion of recommended evaluations between participants currently receiving ERT (43%) and participants not currently receiving ERT (57%) (See Figure 11).

3.6.3.1 Demographics

Analyses failed to identify differences of statistical significance between participants currently receiving and not receiving ERT with regard to demographics and family history. Regression analyses were performed for demographic variables including: age, income, educational background, employment status, marital status, health care coverage, and inability to see a doctor due to cost within the last 12 months. P-values for these variables were adjusted using the Bonferroni correction method for multiple comparisons. Analyses did not identify statistically significant associations with these variables and participants currently receiving or not receiving

ERT. Regression analyses were also performed on variables of family history including whether or not a participant had children affected with Fabry disease and the number of relatives a participant indicated had Fabry disease. Analyses did not identify statistically significant associations with these variables and participants currently receiving or not receiving ERT.

3.6.3.2 Perceived severity

Regression analyses failed to identify differences of statistical significance between participants currently receiving ERT and not currently receiving ERT with regard to perceived severity and degree of worry. Regression analysis was used to determine if severity or worry predicted whether a participant would be currently receiving or not receiving ERT. Analysis using Fisher's exact test failed to identify a statistically significant association between the use of ERT and impact of health beliefs due to diagnosis of Fabry disease.

3.6.3.3 Perceived susceptibility

Analysis using Fisher's exact test was performed to determine if perceived personal susceptibility to Fabry disease symptoms was associated with participants currently receiving ERT and not currently receiving ERT. The p-value for this analysis was adjusted using the Bonferroni correction to a value of 0.003. A relationship with statistical significance was identified for heat/cold intolerance. A trend was found regarding susceptibility to the following symptoms: chronic pain (p-value of 0.006), abdominal pain (p-value of 0.03), burning/numbness/tingling (p-value of 0.01), and diarrhea/constipation (p-value of 0.03) (Table 24). Participants currently receiving ERT were more likely to express personal susceptibility for these five Fabry disease symptoms than participants not currently receiving ERT (Figure 15). Analysis using Fisher's exact test failed to identify differences of statistical significance between participants currently receiving

ERT and not currently receiving ERT with regard to the perceived appropriateness of the term “carrier”.

Table 23. Fisher’s exact test analysis for personal susceptibility and current reception of ERT

| Symptoms | Odds Ratio | 95% CI | p-value |
|---|------------|---------------|---------|
| Chronic pain | 6.35 | (1.44-34.76) | 0.006 |
| Heat/cold intolerance | 11.95 | (2.00-133.32) | 0.002* |
| Abdominal pain | 4.60 | (1.05-24.65) | 0.03 |
| Burning/numbness/tingling | 7.93 | (1.29-89.12) | 0.01 |
| Diarrhea/constipation | 4.19 | (1.01-19.40) | 0.03 |
| *p-value<0.003 is statistically significant | | | |

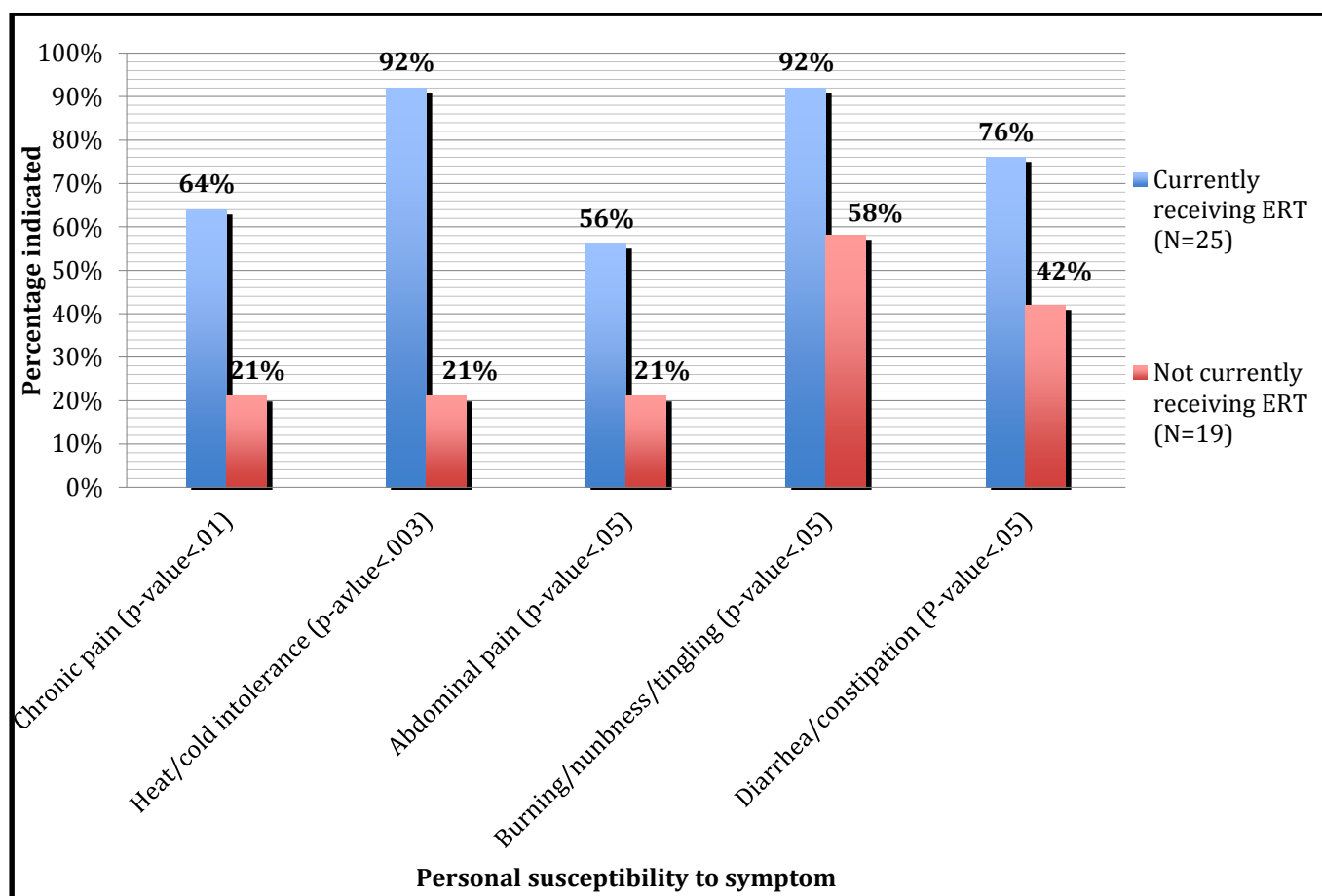


Figure 15. Personal susceptibility to symptoms with a statistically significant difference between participants currently and not currently receiving ERT (N=44)

3.6.3.4 Perceived barriers to treatment, evaluation and monitoring

Analysis using Fisher's exact test failed to identify statistically significant specific barriers to Fabry disease evaluations and monitoring that were associated with participants currently receiving ERT and not currently receiving ERT. The p-value for this analysis was adjusted using the Bonferroni correction to a value of 0.002. A trend was identified between participants currently receiving and not receiving ERT with regard to the percentage who indicated "symptoms not severe" as a barrier (p-value of 0.03) (Table 25). Participants receiving ERT were less likely to indicate "symptoms not severe" than participants not currently receiving ERT (Figure 16).

Table 24. Fisher's exact test analysis for perceived barriers and current reception of ERT

| Barrier | Odds Ratio | 95% CI | p-value |
|---|------------|--------------|---------|
| Symptoms not severe | 0.10 | (0.002-0.91) | 0.03 |
| *p-value<0.002 is statistically significant | | | |

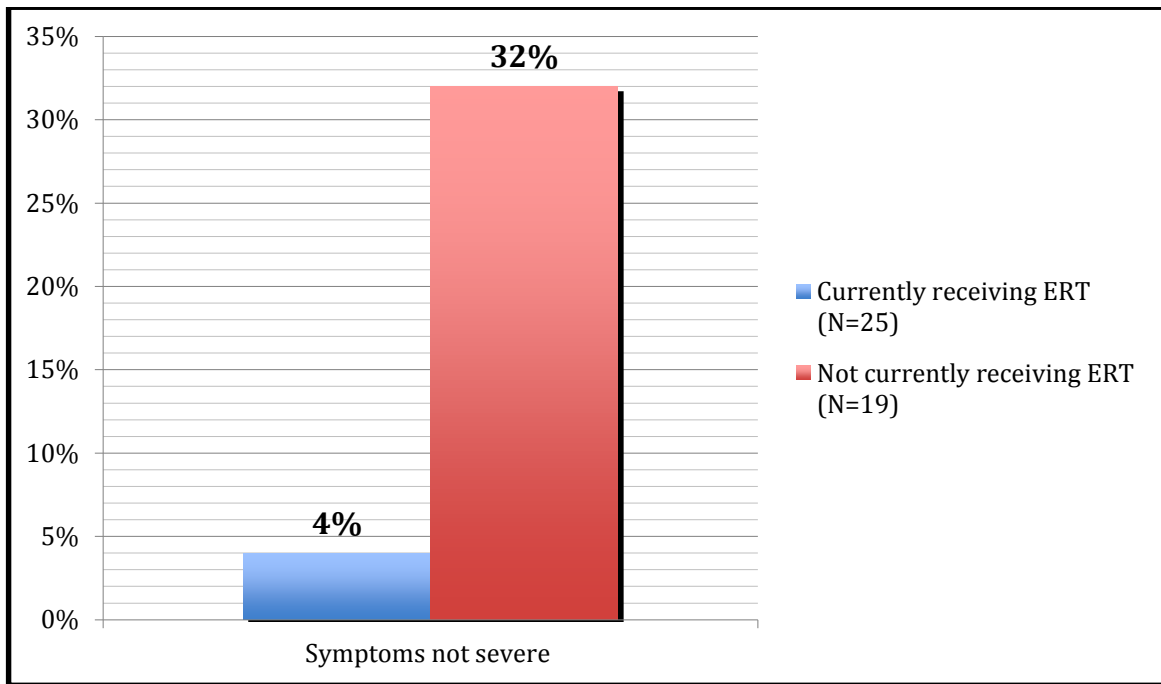


Figure 16. Percentage of participants currently and not currently receiving ERT who indicated “symptoms not severe” as barrier (N=44)

3.6.3.5 Completion of recommended evaluations

Analysis using Fisher's exact test failed to identify differences of statistical significance between participants currently receiving ERT and not currently receiving ERT with regard to the completion of recommended evaluations in the care of Fabry disease.

3.6.4 Modifying variables: participants who indicated no barriers to evaluations and monitoring compared to participants who indicated one or more barriers

Analyses were performed to identify differences in demographics, perceived severity, perceived susceptibility, perceived barriers to treatment evaluation and monitoring, and completion of recommended evaluations between participants who indicated they had no barriers to evaluations and monitoring (36%) and participants who indicated one or more barrier (64%) (Figure 13).

3.6.4.1 Demographics

Regression analyses were performed for demographic variables including: age, income, educational background, employment status, marital status, health care coverage, and inability to see a doctor due to cost within the last 12 months. P-values for these variables were adjusted using the Bonferroni correction method for multiple comparisons. The difference between participants who did and did not indicate barriers to evaluations and monitoring with regard to the demographic variable of household income had a p-value of 0.012 ($p\text{-value} < 0.05$), however, the subsequently adjusted p-value for this variable of 0.008 resulted in this relationship being determined statistically insignificant. Of note, this calculation demonstrated that participants who indicated no barriers to evaluations and monitoring were more likely to have a higher household income than individuals who indicated one or more barrier (Table 26).

Analyses did not identify statistically significant associations with the variables of age, educational background, employment status, marital status, health care coverage, and inability to see a doctor due to cost within the last 12 months and participants who indicated no barriers to evaluations and monitoring and participants who indicated one or more barrier. Regression analysis was also performed on variables of family history including whether or not a participant

had children affected with Fabry disease and the number of relatives a participant indicated had Fabry disease. Analysis did not identify statistically significant associations with these variables and participants who did and did not indicate barrier to evaluations.

Table 25. Regression analysis for level of household income and participants who did and did not indicate barriers to evaluation and monitoring

| Demographic | Coefficient | Error | Z-value | p-value |
|---|-------------|--------|---------|---------|
| Household income | 0.7310 | 0.2908 | 2.514 | 0.0120 |
| *p-value<0.008 for statistical significance | | | | |

3.6.4.2 Perceived severity

Regression analyses failed to identify differences of statistical significance between participants who indicated no barriers to evaluations and monitoring and participants who indicated one or more barrier with regard to perceived severity and degree of worry. Analysis using Fisher's exact test failed to identify a statistically significant association between the presence of self-identified barriers to evaluations and monitoring and impact of health beliefs due to diagnosis of Fabry disease.

3.6.4.3 Perceived susceptibility

Analyses using Fisher's exact test failed to identify differences of statistical significance between participants who indicated no barriers to evaluations and monitoring and participants who indicated one or more barrier with regard to perceived personal susceptibility and the perceived appropriateness of the term "carrier".

3.6.4.4 Proportion currently receiving ERT

Analysis using Fisher's exact test failed to identify statistically significant differences with regard to the proportion of participants on ERT between participants who indicated no barriers to evaluations and monitoring and participants who indicated one or more barrier to evaluations and monitoring.

3.6.4.5 Completion of recommended evaluations

Analysis using Fisher's exact test failed to identify differences of statistical significance with regard to the completion of recommended evaluations between participants who indicated no barriers to evaluations and monitoring and participants who indicated one or more barrier to evaluations and monitoring.

4.0 DISCUSSION

4.1 DEMOGRAPHICS

This study included the assessment of 44 females over the age of 18 with a diagnosis of Fabry disease. Almost all of the study participants were Caucasian and all participants reported a diagnosis of Fabry disease. The median age of participants was 49 years of age, which was higher than the reported median age of females of 38.5 years from the 2012 US Census Bureau data. The majority of participants (approximately 71%) had a total household income greater than \$35,000 and approximately 32% of participants reported a total household income greater than \$75,000, which is comparable to the median household income reported from the 2012 US Census Bureau of \$51,071. In general, participants from this study were more educated and a higher percentage had health care coverage as compared to the 2012 US Census Bureau data. The percentages of participants who had four years of college (Bachelors degree) and graduate level education (Masters or Doctoral degree) were both higher than those reported in the 2012 US Census. In addition, the percentage of participants with health care coverage (95%) was higher than the average reported from the 2012 US Census Bureau (84%). A little over half (56%) of participants were married as compared to 38% of individuals surveyed by America's Families and Living Arrangements (Table 4).

To assess the geographic diversity of the study population, participants were localized into regions of the United States based on the Fabry disease managing center or clinic they indicated on the study questionnaire (Figures 1 and 3 and Table 5). The United States Census Bureau defines a region as a grouping of states that subdivides the nation. The participants were localized in the

United States by region rather than by state or division to better visualize the sample across the nation due to the small size of the study population. It was theorized that the residences of participants were likely within the same region of the United States that their management was conducted. Regions of the United States included the Northeast, South, Midwest, and West (Appendix H). The distribution of the localizable participants based on management site was relatively evenly spread among the Midwest (32%), South (24%), West (16%), and Northeast (15%) (Figure 2).

Information regarding family history was collected for analysis to assess how family history might impact perceived health beliefs and completion of recommended assessments. The majority of participants, approximately 98%, reported a family history of Fabry disease (See Figure 3), which is consistent with the inheritance of Fabry disease as *de novo* mutations are rare.⁵⁹ The majority of participants, approximately 56%, indicated their Fabry disease was maternally inherited (Figure 5). The most common relative with Fabry disease indicated by participants was “mother”, which is consistent with this observation. Interestingly, the five most common relatives (mother, sister, father, son, and daughter) with Fabry disease were all immediate family members to the participants (Table 6). This suggests that at least 47% of participants have witnessed the course of Fabry disease in male and/or female relatives with whom they have likely shared a residence. Approximately 86% of participants with a family history of Fabry disease had a relative who had received ERT (Figure 6). In comparison, 57% of the total participants within the study were personally receiving ERT (Figure 11). Participants who were not currently receiving ERT may have had some degree of familiarity with ERT due to the treatment of a relative.

4.2 SPECIFIC AIM ONE

4.2.1 Administration of survey and questionnaire to 50 females at-risk or diagnosed with Fabry disease

In the aim to recruit 50 female participants this study was unsuccessful. This was likely due to a limitation of the study design in which investigators were unable to directly contact potential participants. In addition, issues with follow-up for interested participants also complicated the ability to recruit and consent the study aim of 50 participants. Two participants who contacted the PI were unable to be re-contacted for study consent due to issues with follow-up. These participants contacted the PI to participate in the study and when the PI attempted to contact the participants, the participants never returned the PI's phone calls.

4.3 SPECIFIC AIM TWO

4.3.1 Characterization of the perceived severity for males and females with Fabry disease

Participants were asked to categorize the severity of Fabry disease for both males and females (Figure 7). The majority of participants (91%) categorized Fabry disease as very serious for males. In contrast, the responses of participants were more varied when asked about the severity of Fabry disease for females. Responses for females included very serious (48%), somewhat serious (18%), and can be, but is not always serious (34%). The diversity of responses for severity in females demonstrates the variability of Fabry disease presentation and progression in females as compared

to males.⁶ Additionally, all participants indicated that Fabry disease was associated with some degree of severity for both males and females. The differences in responses with regard to severity for males and for females, as well as, the fact that no participants thought Fabry disease was not serious for males or female suggests that participants had an appropriate understanding of Fabry disease severity that was consistent with current understanding of the medical community.^{2; 3; 6} These results suggest that these participants have received appropriate information regarding the variability of Fabry disease for females as compared to males.

4.3.2 Characterization of the amount and topics of worry regarding Fabry disease

The majority of participants, approximately 86%, were somewhat to very worried about Fabry disease (Table 7). These results suggest that females with Fabry disease may be significantly burdened by worry. This highlights the need for healthcare providers, such as genetic counselors and/or physicians, to investigate what specific worries their female patients might have in order to better address concerns and improve patient outcomes. Thematic analysis was utilized to identify themes or patterns regarding topics of worry written in response to the open-ended question (Table 8). Many of the topics of worry identified in this analysis are concerns that are able to be addressed or reduced by healthcare providers. Strategies to manage specific concerns of females with Fabry disease are discussed below to provide ways for healthcare providers to reduce the burden of worry for their female patients, potentially improving rapport and communication between patients and providers. In addition, reduction of worry for female patients may reduce barriers to evaluation and treatment for females who are significantly burdened by worry.

Within the responses to the open-ended question, a theme of uncertainty was identified, specifically with regard to symptom development, inheritance, and availability of treatment and

management. Worry due to the uncertainty of symptom development extended to the participant's relatives, as well as the participant herself. This theme further demonstrates an appropriate understanding of the variable presentation and course of Fabry disease for females that was previously noted in assessment of perceived severity.⁶ This variability of disease progression in females and family members, as well as the absence of genotype-phenotype correlation data present challenges to healthcare providers attempting to describe an accurate disease course for females with a *GLA* mutation.⁶ While healthcare providers are limited in their ability to reduce the uncertainty associated with a Fabry disease diagnosis, acknowledgement of this burden may help healthcare providers to better build rapport with their female patients.

In addition to uncertainty of disease progression, analysis demonstrated that the uncertainty associated with potentially passing on Fabry disease to subsequent generations in an individual's family was a source of worry for participants. Discussions regarding current prenatal options to prevent the transmission of a gene mutation to a future family member such as chorionic villi sampling, amniocentesis or pre-implantation genetic diagnosis may help to manage anxiety regarding the uncertain nature of potentially passing on a *GLA* mutation. Discussion of prenatal options are recommended for both males and females with Fabry disease of reproductive age²⁴; however, acknowledgement of these options may also benefit post-menopausal females worried about risks for grandchildren. Recent evidence suggests that a diagnosis of an X-linked condition, like Fabry disease, can have profound and lasting effects on extended family, particularly on grandmothers, who may also benefit from educational measures and genetic counseling.⁶⁰ In addition, education has been associated with increased perceived personal control, defined as "the belief that one has at one's disposal a response that can influence the aversiveness of the event".⁶¹

⁶² Perceived personal control has been implicated as a central means to cope with health threats

including chronic genetic conditions.⁶¹ The promotion of perceived personal control may be particularly effective in addressing this concern of inheritance, as the underlying issue is uncertainty. Education from healthcare providers about risks for family members to have a *GLA* mutation based on X-linked inheritance and about the availability of future treatment options for potentially affected family members may be helpful in decreasing this worry by promoting perceived personal control.

Finally, uncertainty regarding the future availability of treatment and management was also a source of worry for participants. Concerns with regard to treatment and management availability were largely tied to the uncertainty of insurance coverage. Gibas et al. 2008 suggested that genetic counselors can play a role as advocates for females with Fabry disease and this advocacy can include addressing client concerns related to healthcare coverage.⁹ Advocacy by genetic counselors or other healthcare providers may not eliminate this worry, but may prevent or lessen the fear of treatment or management unavailability from being realized.

Another theme identified as a source of worry was premature death. This theme is similar to the awareness of shortened lifespan identified by Kolodny et al. (2002) that contributes to poor quality of life for Fabry disease patients.²⁹ Females are at risk to develop life threatening complications of Fabry disease such as renal failure, stroke, and cardiac complications that could lead to premature death.^{5; 6; 33} While current literature suggests that the lifespans of females are minimally shortened when compared to males, variability of disease symptomology limits the degree of reassurance a health care provider can offer to an individual.^{6; 32} Clarification of the individual's perception of her lifespan may help to address their concerns and recognize when additional therapeutic support should be offered. Also, it is the opinion of this investigator that family history of the individual may act as a modifying variable for the worry of premature death.

The premature deaths of parents, brothers, or other relatives were mentioned throughout the responses of participants in the questionnaires. Clarification of disease progression for males compared to females may help to alleviate this worry for participants whose concern relates to the premature death of a male relative. In addition, the discussion of the variability of disease for females could be utilized as an approach to offer support for females whose concern stems from the premature death of a female relative and a sense of inevitability for their own shortened lifespan. With regard to worry associated with the premature deaths of relatives, disease variability within families and for females in general may still act as a barrier for healthcare providers to address this concern for their female patients.^{6; 22-24} Healthcare providers should initiate conversations with their female patients who express concern for the premature death of one or more relatives to assess whether or not their patients would benefit from therapeutic measures such as support groups or individual therapy.

Additional themes identified in thematic analysis of worry were cost, concern for disease impact on children, and disease progression. Concerns regarding cost were seen throughout analyses in this study and will be discussed further with regard to barriers to treatment, evaluation, and management. Analysis from this study delineates the importance of financial assistance for individuals and families with Fabry disease. The theme of concern for disease impact on children was identified as a source of worry for participants, specifically regarding quality of life for their children. This finding emphasizes the role of a female as both a patient and a caretaker with regard to Fabry disease. Healthcare providers should consider the dual role of patient and caretaker for their female patients when discussing Fabry disease treatment and disease monitoring.

Participants also expressed concern for the progression of Fabry disease in themselves, including the development of more severe disease manifestations such as renal, cardiac, and

cerebrovascular complications. Recent data suggests that early initiation of treatment with ERT is critical to slow the progression of renal symptoms and that ERT provides clinical benefit with regard to cardiac manifestations, pain, and quality of life.³⁷⁻⁴² In order to initiate treatment for a female with Fabry disease and provide clinical benefit for disease manifestations, she must first meet criteria established by Eng et al. (2006) based on degree of symptomology. Degree of symptomology is characterized by the measurement of biomarkers and clinical assessments that are recommended to be performed annually based on published guidelines for the care of females with Fabry disease.⁴ For patients concerned with disease progression, a discussion of the importance of regular evaluations to determine eligibility for ERT, which has the potential to slow the progression of or stabilize renal and cardiac manifestations, may help with compliance for recommended evaluations, as well as provide support for females worried about disease progression. Healthcare providers can utilize this discussion both to reduce worry for their female patients and simultaneously emphasize the importance of clinical evaluations from a perspective unique to females with Fabry disease.

4.4 SPECIFIC AIM THREE

4.4.1 Characterization of perceived susceptibility to Fabry disease manifestations

Perceived susceptibility to Fabry disease symptoms for males and females was calculated from a series of questions in which participants were asked to identify symptoms that males could have and that females could have (Table 13). All of the symptoms participants could select from are symptoms associated with Fabry disease (Table 11). The percentages of symptoms marked for

males compared to symptoms marked for females were equivalent, suggesting that participant's believed that males with Fabry disease and females with Fabry disease are both at risk to develop the same symptoms. Combined interpretation of the analyses for perceived severity and perceived susceptibility illustrates that participants believed that Fabry disease varied in severity for females compared to males, but that both males and females are equally susceptible to Fabry disease symptoms. This understanding of Fabry disease is consistent with the current understanding of the medical community.⁶ Certain symptoms, including pulmonary disease and congestive heart failure, were marked with less frequency than other symptoms for both males and females. As participants were consistent in marking these symptoms with less frequency for both sexes, it is possible that participants were less aware that these symptoms are associated with Fabry disease. Increased education about pulmonary disease and congestive heart failure as Fabry disease manifestations may be needed to address this decreased awareness.

Analysis regarding Fabry disease susceptibility for males and females suggests that participants have an appropriate understanding of Fabry disease risks for females in general. However, comparison of perceived susceptibility of females to perceived personal susceptibility of participants suggests that participants do not apply that same accurate understanding to their own personal risks for the development of Fabry disease symptoms. Analysis showed that participants were more likely to indicate a Fabry disease symptom could develop for females than for themselves personally (Table 14 and Figure 11). Analysis from Part 1 of the three-part project also demonstrated this same phenomenon in which participants indicated an appropriate understanding of the risks for females to develop Fabry disease manifestations, but demonstrated a decreased perceived personal susceptibility to Fabry disease manifestations. In 1999 Lippman described a similar experience in a population of females at increased risk to have a pregnancy

with Down syndrome due to advanced maternal age. Females demonstrated an appropriate comprehension of the risks associated with advanced maternal age, but did not apply that same understanding to their own perception of risk. Lippman (1999) described that these females negotiated with biomedical information by incorporating their own instincts, beliefs and personal experiences into their conception of risk, resulting in a decreased personal perceived susceptibility.⁶³ It is possible that females with Fabry disease similarly incorporate psychosocial and structural modifying variables, such as worry, guilt, or experience with Fabry disease, into their perception of personal susceptibility to Fabry disease manifestations.

It is possible that the difference in perceived personal susceptibility and perceived susceptibility of females demonstrated in this study is the result of the utilization of defense mechanisms, such as denial, by participants in an attempt to cope with their diagnoses. Defense mechanisms are unconscious responses to a real or perceived threat that attempt to maintain some measure of control and reduce painful or uncomfortable emotions.⁶⁴ Denial of personal risk for Fabry disease symptoms, which was self-identified by a participant as a barrier to evaluation and treatment (Table 19), may be an explanation for this difference in perception of disease susceptibility. Denial of symptoms would include rejecting the possibility that an individual has or could develop symptoms. Furthermore, approximately 16% of participants indicated that their symptoms were not severe and that this lack of severity acted as a barrier for the completion of recommended assessments (Table 18). It is possible that females with these barriers would not comply with recommended evaluations and treatment, as they would not perceive personal benefit from these assessments.

Results from this current study provide evidence that females with Fabry disease are appropriately educated about the risks to develop Fabry disease manifestations, but that this

education is not incorporated into their perception of personal susceptibility to Fabry disease manifestations. These results suggest that investigation of perceived personal susceptibility by healthcare providers is warranted even if a female patient communicates an appropriate understanding of risk for females with Fabry disease. Lippman (1999) suggests that practices of genetic counselors including active listening and discussion rather than education are critical to address the incorporation of modifying variables such as instincts, beliefs, and personal experiences in the perception of susceptibility.⁶³ In addition to educating female patients about risks for symptom development, health care providers should employ active listening and engage female Fabry disease patients in conversation to identify possible modifying variables, including personal beliefs, burden, experiences, and coping mechanisms such as denial, that may be impacting perceived personal susceptibility. Healthcare providers may then be able to address these modifying variables and potentially recognize the decreased perceived personal susceptibility demonstrated in this analysis.

Differences of statistical significance between susceptibility of females in general and participants personally were observed for the symptoms of proteinuria, congestive heart failure, enlargement of heart, stroke, chronic pain, abdominal pain, angiokeratomas, kidney failure, heart attack, transient ischemic attack, problems with sweating, corneal whorls, and depression and anxiety. The four symptoms of pulmonary disease (p-value of 0.0098), heat/cold intolerance (p-value of 0.0269), abnormal heart rhythm (p-value of 0.0162), and burning/numbness/tingling (p-value of 0.0133) demonstrated the trend described above in which participants were more likely to indicate a Fabry disease symptom could develop for females than for themselves personally. Even though effects of nominal significance were observed for these symptoms, none of the results met the stricter threshold for statistical significance after adjustment of the number of tests were

considered. This was likely due to the small population size of this study. Further investigation may help to determine if participants feel more personal susceptibility to these symptoms than to the other Fabry disease symptoms.

4.4.2 Assessment of the term “carrier”

Analyses were completed to determine the usage and perceived appropriateness of the term “carrier” (Figure 10). Approximately 60% of participants had used the term “carrier” to describe themselves at some point in time compared to 40% of participants who currently believed the term was an inappropriate description of themselves. This difference in personal usage and perceived appropriateness of the term “carrier” in combination with written justifications provided by participants suggests that some of these participants may have used the term “carrier” to describe themselves in the past and not currently. Additionally, approximately 77% of participants indicated that a physician or healthcare provider at some point in time had used the term “carrier” to describe them. The term “carrier” was still considered an appropriate term for heterozygous females by the medical community as recently as 2001.⁵ As there was no assessment of time or date with regard to usage of the term “carrier” by providers or participants, it is difficult to determine if healthcare providers had inappropriately labeled participants as a “carrier” based on the data collected. Further investigation into how recently participants had been referred to or referred to themselves as “carriers” is needed in order to appropriately assess current usage of the term “carrier”.

The majority of participants, approximately 60%, indicated that they believed the term “carrier” was an inappropriate description of their disease status. Qualitative thematic analysis was utilized to examine responses between participants who perceived the term “carrier” as

appropriate and among those who perceived it as inappropriate (Table 15). The analysis suggests a difference in the understanding of the meaning of the term “carrier” among participants who did and did not self-identify as “carriers”. Participants who believed the term was inappropriate had a similar understanding of the meaning of the term “carrier” as the medical community, in that the term “carrier” denotes a lack of symptoms.^{5;34} In contrast, participants who believed the term was appropriate did not share this understanding and believed that the term “carrier” meant the ability to pass on the disease independent of the ability to develop symptoms. This analysis suggests that a female who self-identifies as a “carrier”, or perceives the term “carrier” as an appropriate description of herself, does not necessarily believe she is not at risk for or does not currently have Fabry disease symptoms. Patient perceived appropriateness of the term “carrier” may not be a good indicator of perceived personal susceptibility as some patients may not believe this term reflects their ability to develop or have Fabry disease symptoms. Healthcare providers should either clarify their meaning of the word “carrier” to female patients or ask females to clarify their understanding of the word “carrier” to prevent possible miscommunication. For newly diagnosed female patients, healthcare providers could also initiate a discussion about the history of the term “carrier” within the Fabry disease community and the potential to encounter this term as a description for females with a *GLA* mutation on the Internet or in the literature. This discussion may help to provide context regarding the usage of the term “carrier” to describe females with Fabry disease and prevent potential miscommunications between healthcare providers and their patients.

4.5 SPECIFIC AIM FOUR

4.5.1 Characterization of perceived benefits of treatment, evaluations and monitoring

More than half of participants, approximately 57%, were currently receiving ERT (Figure 13). These participants were asked to describe their expectations of ERT in response to an open-ended question (Table 16). Expectations described by participants were compared to known outcomes of ERT reported in the literature. Expectations described by participants that are consistent with current literature regarding the clinical benefits of ERT are considered realistic or appropriate expectations, while expectations that are incongruent with the literature are considered unrealistic or inappropriate. Expectations listed by patients such as to feel better and to have more energy are issues related to quality of life, which can be improved with ERT.^{40; 41} Additionally, expectations that ERT would stabilize organ damage, specifically kidney and heart, are also consistent with the current understanding of the effectiveness of ERT, although stabilization of renal and/or cardiac damage is not achieved in every individual who receives ERT and may depend on when ERT is initiated in the disease course.^{37-39; 42} The interpretation of the appropriateness of the expectation “improve symptoms” depended to a degree on the specificity of the individual responses of the participants who described this expectation. For example, the expectation that ERT would improve all symptoms is not supported by current data. However, the expectations that ERT would improve pain and proteinuria are consistent with current evidence.³⁷⁻⁴¹ Expectations listed by participants including prevention of symptoms, specifically stroke and renal, and prolongation of life are controversial in nature and have yet to be proven as benefits of ERT.^{7; 12} The expectation that ERT would cause an individual to lose weight could not be corroborated by literature review.

Not all of the expectations described by participants were consistent with known clinical benefits associated with initiation of ERT, suggesting that further education about the benefits and limitations of ERT to female patients may be needed. Discussions of the specific benefits and limitations of ERT, as well as the tests used to measure effectiveness of ERT should take place between healthcare providers and females who meet criteria to receive ERT. Furthermore, healthcare providers should investigate what specific symptoms females might expect to improve in order to better assess if the expectation of “improve symptoms” is realistic for their individual patients. By assisting their patients to set appropriate expectations, healthcare providers may improve the perceived benefit to treatment with ERT by preventing the formation of unattainable expectations.

Qualitative thematic analysis was utilized to determine if participants currently receiving ERT had a positive or negative experience based on the nature of the language used by participants in description of their ERT experience (Figure 12). A significant amount of participants, approximately 37%, used negative language to describe their experience with ERT. These participants communicated frustration with ERT and indicated feeling worse after initiation of ERT. In addition, 14% of participants seemed to be grappling with their experience. These participants either were unsure about how to feel about their experience being treated with ERT or used a combination of both positive and negative language when describing ERT. Therefore, approximately 51% of participants did not seem to have a positive experience with ERT and may not perceive benefits to treatment based on this analysis. Efforts can be made by healthcare providers to explore their female patients’ satisfaction with ERT and to attempt to address issues or misconceptions that could lead to decreased perceived benefit.

4.6 SPECIFIC AIM FIVE

4.6.1 Characterization of perceived barriers to treatment, evaluations and monitoring

Participants were asked to indicate what barriers prevented them from completing recommended evaluations and monitoring. The aim was to identify the most common barriers to females with Fabry disease in order to develop strategies and interventions to reduce possible barriers. Interestingly, a significant proportion of participants, approximately 36%, indicated that they had no barriers to treatment and evaluation (Figure 13). This proportion is larger than was expected based on the clinical experience of investigators. Of the 64% of participants who indicated at least one or more barrier to evaluations, the most common barrier, indicated by approximately 36% of participants, were costs not covered by insurance (Table 18). These costs were identified by participants as prescriptions unrelated to ERT, copays, high deductibles, and costs of examinations and evaluations (Table 20). Cost was not only identified as a barrier for participants, but also as a significant source of worry (Table 8). Issues related to financial concerns were previously identified as a barrier to ERT⁴³; however, analyses in this study suggest that the burden of cost may be underappreciated by healthcare providers. As females with Fabry disease play both the role of patient and caretaker, costs are incurred from personal healthcare as well as from healthcare of relatives. Healthcare providers can make efforts to make patients and families aware of financial assistance resources to help decrease this barrier. Organizations such as Patient Services, Inc. (<https://www.patientservicesinc.org/>) that provide financial assistance for insurance deductibles, co-payments, and incidental medical expenses should be offered by healthcare providers as resources for patients with issues regarding costs not covered by insurance.

Other barriers indicated with increased frequency by participants included distance from centers (approximately 30%), anxiety (approximately 25%), and feeling overwhelmed (approximately 20%). Distance from centers may be a difficult barrier for healthcare providers to address for all patients, as it is relative to the patient and the clinic resources. This analysis does suggest that the facilitation of homecare, when possible, for those females receiving ERT may be important to decrease the barriers of distance. For all patients regardless of treatment status, assistance with costs associated with distance and travel including gas and parking may be an alternative means to address this barrier. Anxiety can be both a disease feature of Fabry disease and a secondary complication from increased worry.²⁹ Treatment with medication or evaluation by a psychiatrist or psychological counseling may help females with chronic anxiety and it is important for the Fabry healthcare professionals to assess this possibility and provide patients with referral information when appropriate. In addition, healthcare providers may be able to reduce the barriers of anxiety and feelings of being overwhelmed by using the aforementioned strategies discussed above to reduce worry prior identified in this analysis and discussing reasonable expectations and goal setting.

Guilt was identified with less frequency in this analysis; however, it was identified throughout the responses of open-ended questions pertaining to worry and feelings after diagnosis. Guilt was also identified in the Part 1 study as a significant barrier to evaluation and treatment. Guilt may be difficult for participants' to self-identify in this format and may be better assessed and addressed in the form of personal interview. Although guilt was not identified as a common barrier within this analysis, the identification of guilt in the Part 1 study as well as within the open-ended responses in this project delineate the important role that guilt may play in the formation of the perceived health beliefs of females with Fabry disease. Feelings of guilt have been associated

with a diagnosis of Fabry disease and may impact the willingness of females to complete recommended evaluations.²⁴ As personal interviews may be a more effective format to address guilt than a written survey, healthcare providers may want to engage their female patients in a discussion about guilt to assess if it may be acting as a barrier to treatment and/or evaluation.

4.7 SPECIFIC AIM SIX

4.7.1 Modifying variables and cues to action: completion of recommended evaluations

In order to assess compliance for females with Fabry disease, participants were asked to indicate what evaluations were recommended to them by healthcare providers and which of those evaluations they had completed both at the time of diagnosis and on a regular basis. All of the evaluations listed for participants in the questionnaires were consistent with current guidelines for the management of females with Fabry disease described by Eng et al. (2006), except for the evaluation “kidney biopsy”.⁴ Kidney biopsies may be useful as a baseline assessment and in atypical presentations. Repeat kidney biopsy is useful when disease is progressing despite therapy.⁶⁵ For this reason, baseline kidney biopsies are often recommended by medical providers when initiating females on ERT. Interestingly, none of the evaluations recommended to participants were observed with a 100% frequency, suggesting that none of the evaluations were recommended to all of the participants (Table 22). This observation was unexpected as all of the evaluations should be recommended to all females with Fabry disease in accordance with recommended guidelines.⁴ Issues with recall bias, however, may be obscuring the true percentages of evaluations recommended to participants. Assessment of the physicians and healthcare

providers managing Fabry disease for these participants may provide some clarification as to whether or not the lower percentages of recommended evaluations were due to physician error, recall bias, or to personal medical circumstances of patients. Clarification as to the explanation for the reduced frequencies of recommended evaluations may help to determine if further education of healthcare providers regarding the recommended guidelines for the management of females with Fabry disease is indicated.

In general, recommended evaluations were more often completed after diagnosis than on a continuous basis (Figure 14). The reason for this trend may be due to increased motivation from feelings at diagnosis including fear or concern for self. It is also possible that participants perceived increased benefits and/or decreased barriers to evaluations and monitoring at the time of diagnosis compared to later in management. Assessment of females soon after diagnosis may bring clarification to these possible explanations. Certain evaluations including electrocardiogram, echocardiogram, and lipid panel were completed more often on a continuous basis than at diagnosis. It is possible that the evaluations excluding the lipid panel, electrocardiogram, and echocardiogram were perceived as too cumbersome or time consuming to complete on a regular basis. Perhaps participants did not remember the completion of a lipid panel at the time of diagnosis, as it is a less invasive test compared to the other evaluations. Alternatively, it is possible that physicians order a lipid panel more often at subsequent visits than at the time of diagnosis. Electrocardiograms and echocardiograms are both evaluations that assess cardiac manifestations. These evaluations were both recommended with frequencies of 95% and 93% respectively. These observations suggest that healthcare providers and participants may be particularly concerned with the development of cardiac manifestations.

Analyses failed to identify a statistically significant difference between evaluations recommended to and completed by participants. Some statistical evidence of decreased completion of recommended evaluations was noted for the evaluations of 24-hour holter monitor (p-value of 0.0079), brain MRI (p-value of 0.0067), Fabrazyme antibody (p-value of 0.0228), and heart MRI (p-value of 0.0352) (See Table 22). Even though effects of nominal significance were observed for these evaluations, none of these results met the more conservative threshold for Bonferroni adjustment. The evaluations of 24-hour holter monitor, brain MRI, and heart MRI are typically considered time consuming and cumbersome examinations by patients. The burden associated with these evaluations may act as a barrier to participants and provide an explanation for the trend described above. Fabrazyme antibody, however, is a blood test used to evaluate the development of antibodies to treatment with ERT in individuals receiving ERT and is minimally invasive as compared to other evaluations.⁴ It is possible that participants did not recall that this test was performed during a clinical visit as it is less invasive, providing an explanation for the trend for this evaluation described in analysis.

The potential effect of recall bias and its effect on the true percentages of evaluations recommended to participants may be complicating analysis of the completion of recommended assessments. Further investigation into the completion of recommended evaluations should be pursued to confirm that females with Fabry disease truly do not have difficulties with compliance for recommended evaluations. In addition, perceived severity for females with Fabry disease, amount of worry, and perceived personal susceptibility to Fabry disease manifestations were not associated with completion of recommended assessments.

4.7.2 Modifying variables: the impact of a diagnosis of Fabry disease

All of the participants within the study reported a diagnosis of Fabry disease. Thematic analysis was utilized to identify themes within the responses to the open-ended question regarding patients' feelings after their diagnosis (Table 22). Participants expressed that at the time of diagnosis they experienced concern for children and other relatives in addition to personal concerns about prognosis. These themes and the reported emotions of sadness, fear, guilt, and dread related to the diagnosis have been described within the literature regarding diagnoses of genetic conditions, providing further evidence that these emotions are associated with a diagnosis of Fabry disease.²⁴ Healthcare providers should continue to acknowledge these emotions as potential reactions to a diagnosis.

Of note, not all feelings and emotions after diagnosis described by participants were negative. A theme of validation was identified at the time of participants' diagnoses. These participants described relief in learning the cause of their personal symptoms or family history, as well as a sense of validation in confirming that their symptoms were not imagined. Females with Fabry disease have an average 16.3-year delay in diagnosis from symptom onset due to diversity and non-specificity of symptoms and are more likely than males to be labeled as problem patients leading to dismissal by healthcare providers.^{6; 9; 35} This analysis suggests that the participants may have experienced these same issues described in the literature and that diagnosis provided a resolution to resulting frustrations. Healthcare providers should therefore not presume that all feelings resulting from diagnosis will be negative. The three themes of concern for children and other relatives, concern for self, and validation were often expressed simultaneously in participants' responses, signifying the complexity of emotions felt at the diagnosis. Knowledge of these issues may help health care providers to be better prepared to address these concerns at

the time of diagnosis or in subsequent visits, helping providers to build rapport and improve communication with their female patients.

In addition to the themes discussed above, a theme of indifference was identified for participants diagnosed in childhood, for those labeled incorrectly as asymptomatic carriers at the time of diagnosis, and for those participants who anticipated that they would be diagnosed with Fabry disease. With the increase of newborn screening initiatives in the United States, diagnoses of Fabry disease may be occurring at younger ages in the future. It is possible that feelings of indifference or delayed reaction toward a diagnosis of Fabry disease may increase in the future due to increased diagnoses at younger ages. However, as literature continues to provide evidence of heterozygous females with significant Fabry disease manifestations, participants may be less likely to feel indifferent about a diagnosis of Fabry disease due to incorrect labeling as a carrier. The education of healthcare providers, however, is critical in the reduction of females being mislabeled as carriers not at risk for disease manifestations.

The majority of participants, approximately 75%, reported that their diagnoses of Fabry disease impacted their ideas about their health (Figure 15). Thematic analysis was performed on responses to the open-ended question to determine the ways in which health beliefs were impacted (Table 22). The theme of hyperawareness of health issues seemed to burden participants who described this experience. Healthcare providers may be able to lessen this burden by helping patients to identify what symptoms may be related or unrelated to Fabry disease as symptoms are often diverse and nonspecific.⁶

Changes in healthcare practices were also identified as a theme for participants whose health beliefs were impacted. These changes mostly included alterations in diet and increased exercise. While certain diets and exercise practices are associated with decreased risk for chronic

health conditions including cardiovascular disease and diabetes mellitus type 2 and are generally recommended by organizations including the World Health Organization (WHO), the United States Department of Agriculture (USDA), and the United States Department of Health and Human Services (HHS), their benefits have yet to be recognized for the prevention or treatment of chronic genetic conditions such as Fabry disease. Healthcare providers may want to provide clarification about the health concerns targeted by these interventions and explain to patients that these changes may help to prevent the development of compounding chronic health conditions, but will not specifically prevent or treat Fabry disease complications in order to reduce or prevent frustrations resulting from ineffective health practices.

A theme of change in perception of health was identified for participants. Changes in perception of health expressed by participants including shortened lifespan and reduced quality of life are consistent with current literature that states that females with Fabry disease have poor self-perception of health and reduced quality of life.^{5; 48} In addition to these negatively associated changes in perception of health, this study also identified a positive impact on perception of health. Similar to the theme of validation identified in feelings at the time of and after diagnosis, participants expressed relief in understanding the cause of their health concerns and an appreciation of being able to better comprehend their health issues and the health issues of family members. Educating patients about Fabry disease may help participants to correct misunderstandings of disease that could lead to poor self-perception of health or to replace a poorer self-perception of health with an improved understanding of health.

Another theme with regard to impact on health beliefs was increased worry regarding insurance and work discrimination, long-term issues resulting from Fabry disease, and inevitable deterioration of health. These concerns relate to topics of worry identified in the thematic analysis

of topics of worry about Fabry disease described in Specific Aim Two. Long-term issues and deterioration of health relate to the prior identified theme of disease progression as a source of worry. Additionally, insurance and work discrimination concerns relate to uncertainty related to the availability of treatment and management options, which was largely associated with insurance coverage. These concerns are focused on potential financial barriers to treatment, evaluations and monitoring. This analysis provides further evidence that females with Fabry disease are significantly impacted by worry, particularly regarding the inevitability of disease progression and financial concerns associated with treatment and management.

Analysis from this study suggests that reactions to diagnosis are complex in nature and include emotions ranging from sadness to relief and validation. Female patients may feel a combination of concerns for both their own health and the health of their relatives. Reviewing the impact of the diagnosis on the personal management for female patients, as well as the potential impact for their relatives may be important to comprehensively address patient concerns. In addition, female patients may feel a sense of validation from their diagnosis and healthcare providers can acknowledge and encourage this reaction to increase potential positive reactions to diagnosis. Healthcare providers should also be aware patients diagnosed at younger ages may adjust to diagnoses differently than individuals diagnosed in adulthood. Diagnoses of Fabry disease have the potential to impact female patients' ideas about their health. Education about symptoms associated with Fabry disease and the appropriate management and treatment of these symptoms may reduce misconceptions that lead to poor self-perception of health and frustration from the utilization of ineffective healthcare practices. The impact of worry, specifically regarding disease progression and financial concerns associated with treatment and management, may serve as a significant burden to females with Fabry disease. Healthcare providers should utilize

strategies discussed within “perceived severity” (Specific Aim Two) to address these concerns including the discussion of treatment with ERT for females and their relatives and the discussion of resources for financial assistance.

4.7.2.1 Modifying variables: participants currently receiving ERT compared to participants not currently receiving ERT

Analyses of perceived severity, perceived susceptibility, perceived barriers to evaluations and monitoring, and completion of recommended evaluations were performed to characterize potential differences between participants currently receiving and not receiving ERT. A trend was identified in which participants receiving ERT felt more personally susceptible to the symptoms of chronic pain (p-value of 0.006), heat/cold intolerance (p-value of 0.002), abdominal pain (p-value of 0.03), burning/numbness/tingling (p-value of 0.01), and diarrhea/constipation (p-value of 0.03) (Table 24 and Figure 15). Perceived personal susceptibility is defined in this analysis as to have or feel likely to develop a symptom. The symptoms listed above are not considered life-threatening manifestations of Fabry disease, but are all associated with poor quality of life.⁴⁸ This trend suggests that perceived susceptibility for symptoms associated with quality of life may be higher in females receiving ERT than those not receiving ERT. Females receiving ERT must meet criteria established by Eng et al. (2006) based on measurements and evaluations largely related to life-threatening cardiac, renal, and cerebrovascular manifestations. The presence of chronic acroparasthesias resistant to conventional therapy or of chronic or disabling gastrointestinal distress are the only criteria for ERT initiation related to quality of life.⁴ Thus, participants receiving ERT most likely had symptoms of renal, cardiac, or cerebrovascular manifestations of Fabry disease, as well as the aforementioned symptoms related to quality of life. Of note, early signs of renal or cardiac disease such as proteinuria or mild left ventricular hypertrophy, in contrast

to the symptoms associated with quality of life, may not produce symptoms experienced by a patient. This evidence brings into question whether symptoms associated with quality of life, or even more simply that symptoms that are noticeable to patients, are stronger motivators for treatment with ERT than life-threatening symptoms that might qualify a female for treatment. Healthcare providers may want to emphasize the ability of ERT to treat symptoms associated with quality of life in discussions regarding the potential initiation of ERT for their female patients as these symptoms may act as internal cues to action for the initiation of ERT.^{40; 41} While this trend is very compelling for the symptoms of chronic pain, abdominal pain, burning/numbness/tingling, and diarrhea/constipation, the associated p-values do not meet the stricter threshold for statistical significance.

Participants currently receiving ERT indicated the barrier of “symptoms are not severe” with less frequency than participants not receiving ERT (p-value of 0.03) (Table 25 and Figure 16). This observation is logical, as females receiving ERT must have symptoms considered significant enough to warrant initiation of ERT.⁴ While this observation does show some degree of nominal significance, it does not meet the more conservative threshold for statistical significance after adjustment for the number of tests considered.

4.7.2.2 .Modifying variables: participants who indicated no barriers to evaluations and monitoring compared to participants with one or more barrier

Analyses of perceived severity, perceived susceptibility, current treatment with ERT, and completion of recommended assessments were performed to characterize potential differences between participants with and without barriers to evaluations and monitoring. A trend was observed in which participants who indicated no barriers to evaluations and monitoring had a higher income than those participants who indicated one or more barrier to evaluations and

monitoring (p-value of 0.012). This observation is of particular interest as the most frequent barrier indicated by participants was related to cost, providing further evidence that cost is a significant burden for females with Fabry disease and that efforts should be made by healthcare providers to provide resources for financial assistance to their female patients with Fabry disease. While this trend seems compelling, it fails to meet the conservative threshold for Bonferroni adjustment.

4.8 LIMITATIONS

This study was not without limitations. The small population size of the study limits the power of the analysis. Both the study design in which investigators could not directly contact potential participants and the rarity of the condition constrained the ability of investigators to acquire a larger study population. Certain limitations are inherent in the study design. Self-reporting of personal medical information is subject to recall bias. The open-ended format of certain questions, while critical to the characterization of the health beliefs of females, occasionally resulted in participants describing an experience unrelated to the question. This led to the exclusion of certain responses from qualitative thematic analysis. In addition, investigators re-contacted three participants for clarification about responses for the questions assessing perceived susceptibility and perceived severity for males. These participants did not believe they were supposed to answer those questions at the time they completed the questionnaire. There was an inability to confirm reported diagnoses of Fabry disease. However, it is unlikely that participants incorrectly labeled themselves as diagnosed with Fabry disease as a diagnosis of Fabry disease was defined for participants.

Approximately 14% of participants could not be localized into a region of the United States based on management location due to issues such as lack of current management or non-localizable management, an example being the Lysosomal Storage Disease Clinical Care Network which has numerous clinics located within multiple regions of the United States. This inability demonstrates a limitation of this methodology. In addition, this analysis suggested that this study succeeded in recruiting participants with a relatively even distribution from four regions of the United States (Northeast, South, Midwest, and West); however, not all divisions, defined by the US Census Bureau as small groupings of states within a region, are equally represented. This is a limitation of the small population size of the study. Finally, there was a limitation inherent in the analysis of perceived susceptibility to Fabry disease manifestations. In the questionnaire participants were asked to indicate what symptoms could develop, or were “possible”, in females with Fabry disease. In contrast, participants were then asked to indicate what symptoms were “likely” to develop for them selves. It is possible that participants perceived these two questions differently and that the difference in perceived personal susceptibility as compared to perceived susceptibility of females described in this analysis was partially due to the different wording of the two questions. It is unlikely, however, that this would entirely explain the statistically significant differences between the perceived susceptibility of females and perceived personal susceptibility as the p-value for statistical significance was adjusted to a more conservative value. In addition, this phenomenon was also identified in Part one analysis of the three-part study and has also been reported among another population of at-risk females within the literature,⁶³ providing further evidence that the difference wording may not be the explanation for the differences in perceived susceptibility.

5.0 CONCLUSIONS

This study was unable to recruit the first specific aim of 50 study participants, however, this inability was likely due to limitations within the study design and regarding the study of a rare genetic disease.

The second specific aim of this study was to characterize the perceived severity of females with Fabry disease. Analysis from this study demonstrates that participants had an appropriate understanding of Fabry disease severity for both males and females, suggesting that current educational measures are successfully communicating the variability of Fabry disease for females as compared to males. In addition, female patients may be significantly burdened by worry, highlighting the need for healthcare providers to investigate the specific worries that burden their female patients. Healthcare providers should engage their female patients in conversation about potential sources of worry as the majority of sources of worry identified from this analysis may be able to be addressed and/or reduced by healthcare providers using a variety of different strategies. Reduction of worry for female patients may lead to improved rapport and communication, and the potential reduction of barriers to evaluations and treatment.

The third specific aim of this study was to characterize the perceived susceptibility of females to Fabry disease manifestations. Results from this study provide evidence that females with Fabry disease are appropriately educated about the risks to develop Fabry disease manifestations, but that they view their personal susceptibility in a different manner. These results suggest investigation by healthcare providers is warranted to assess personal perceived susceptibility even if a female patient communicates an appropriate understanding of risk for females with Fabry disease. In addition to educating female patients about risks for symptom

development, health care providers should employ active listening and engage female Fabry disease patients in conversation to identify possible modifying variables, including personal beliefs, burden, experiences, and coping mechanisms such as denial, that may be impacting perceived personal susceptibility. Healthcare providers may then be able to address these modifying variables and potentially address the decreased perceived personal susceptibility demonstrated in this analysis. In addition, analysis regarding the perceived appropriateness of the term “carrier” suggests that a female who self-identifies as a “carrier”, or perceives the term “carrier” as an appropriate description of herself, does not necessarily believe she is not at risk for or does not currently have Fabry disease symptoms. Patient perceived appropriateness of the term “carrier” may not be a good indicator of perceived personal susceptibility as some patients may not believe this term reflects their ability to develop or have Fabry disease symptoms. Healthcare providers should either clarify their meaning of the word “carrier” to female patients or ask females to clarify their understanding of the word “carrier” to prevent possible miscommunication.

The fourth specific aim of this study was to characterize the perceived benefits to treatment with ERT. Not all of the expectations of ERT described by participants were consistent with known clinical benefits associated with initiation of ERT, suggesting that further education about the benefits of limitations of ERT is needed for females with Fabry disease. Discussions of the specific benefits and limitations of ERT, as well as the tests used to measure the effectiveness of ERT should take place between healthcare providers and females who meet criteria to receive ERT. By assisting their patients to set appropriate expectations, healthcare providers may improve the perceived benefit to treatment with ERT by preventing the formation of unattainable expectations. In addition, a number of participants demonstrated a negative experience with ERT or seemed to be grappling with how to feel about their experiences being treated with ERT. This

analysis suggests that some female patients may not perceive benefits to treatment due to issues with frustration, feeling worse, or uncertainty of expectations. Efforts can be made by healthcare providers to explore their female patients' satisfaction with ERT and to attempt to address issues or misconceptions that could lead to decreased perceived benefit.

The fifth specific aim of this study was to characterize the perceived barriers to treatment and evaluations for females with Fabry disease. Analyses from this study suggest that the burden of cost may be underappreciated by healthcare providers. Healthcare providers can make efforts to make patients and families aware of available financial assistance resources to help decrease this barrier. In addition, distance from centers, anxiety, and feeling overwhelmed may also act as barriers for females with Fabry disease. Healthcare providers can utilize a variety of approaches to reduce these barriers including providing financial assistance for travel and by facilitating homecare for females receiving ERT, as well as by employing strategies to reduce sources of worry such as education, advocacy, and referral to counseling services..

The sixth specific aim was to characterize differences among the study population that may affect health beliefs, including potential modifying variables and cues to action. Analyses failed to identify a difference of statistical significance between evaluations recommended to and completed by participants. Issues with recall bias, however, may be obscuring the true percentages of evaluations recommended to participants. Assessment of the physicians and healthcare providers managing Fabry disease for these participants may provide some clarification as to whether or not the lower percentages of recommended evaluations were due to physician error, recall bias, or to personal medical circumstances of patients. Clarification as to the explanation for the reduced frequencies of recommended evaluations may help to determine if further

education of healthcare providers regarding the recommended guidelines for the management of females with Fabry disease is indicated.

Analysis from this study suggests that reactions to diagnosis are complex in nature and may impact the health beliefs of a patient. Female patients may feel a combination of concerns for both their own health and the health of their relatives. Reviewing the impact of the diagnosis on the personal management for female patients, as well as the potential impact for their relatives may be important to comprehensively address patient concerns. In addition, female patients may feel a sense of validation from their diagnosis and healthcare providers can acknowledge and encourage this reaction to increase potential positive reactions to diagnosis. Healthcare providers should also be aware patients diagnosed at younger ages may adjust to diagnoses differently than individuals diagnosed in adulthood. Education about symptoms associated with Fabry disease and the appropriate management and treatment of these symptoms may reduce misconceptions that lead to poor self-perception of health and frustration from the utilization of ineffective healthcare practices.

Analyses were performed to characterize potential differences among females currently receiving ERT and not currently receiving ERT as treatment with ERT was theorized as a possible modifying variable for females with Fabry disease. Analysis identified that participants currently receiving ERT typically had greater perceived susceptibility to symptoms associated with quality of life than participants not currently receiving ERT. This evidence brings into question whether symptoms associated with quality of life, or even more simply that symptoms that are noticeable to patients, are stronger motivators for treatment with ERT than life-threatening symptoms that might qualify a female for treatment. Healthcare providers may want to emphasize the ability of ERT to treat symptoms associated with quality of life in discussions regarding the potential

initiation of ERT for their female patients as these symptoms may act as internal cues to action for the initiation of ERT.

Finally, analyses were performed to identify potential modifying variables for participants who indicated no barriers to evaluations and monitoring as compared to participants who indicated one or more barrier to evaluations and monitoring. A trend was observed in which participants who indicated no barriers to evaluations and monitoring had a higher income than those participants who indicated one or more barrier to evaluations and monitoring, providing further evidence that cost is a significant burden for females with Fabry disease and that efforts should be made by healthcare providers to provide resources for financial assistance to their female patients with Fabry disease.

6.0 FUTURE RESEARCH OPPORTUNITIES

This study is a part of a larger three-part project aimed at assessing both the health beliefs of females diagnosed and at-risk for Fabry disease and the beliefs of medical providers about the importance of clinical evaluation, continued monitoring, and treatment for these females. The future study (Part 3) will aim to characterize the beliefs of medical providers about the importance of clinical evaluation, continued monitoring, and treatment for diagnosed or at-risk females, as well as to assess provider adherence to published recommendations for the management of females. A modified questionnaire will be created to assess healthcare providers listed by participants in this current study (Part 2) to maintain continuity of this project. Future assessment of the beliefs of healthcare providers will provide clarification regarding potential recall bias regarding evaluations recommended to participants from this current study, as well as allow for further investigation of the current usage and perceived appropriateness of the term “carrier” by healthcare providers. Combined analysis from all three parts of this project will provide a comprehensive investigation into the health beliefs of both adult females with Fabry disease and the healthcare providers who manage them, leading to the identification of sources of miscommunication and potential barriers for both females patients and healthcare providers that may lead to poor patient outcomes. Increased awareness of patient and provider miscommunication and barriers, as well as strategies developed to address burdens, common sources of misunderstandings, and barriers have the potential to improve communication between patients and their healthcare providers and ultimately lead to improved patient outcomes.

In addition to the completion of Part 3 of this project, data from this analysis could be used to create a revised questionnaire utilized in the clinical setting by healthcare providers, such as genetic counselors or physicians, as a means to initiate a dialogue about potential worries, perceived susceptibility, and perceived benefits and barriers to treatment, evaluation and monitoring. Future studies could be pursued to assess the effectiveness of the revised questionnaire in addressing issues for females diagnosed with Fabry disease and the reduction of perceived barriers by using a survey to determine perceived improvement in patient-provider interactions, compliance to recommended evaluations and treatment, and perceived reduction of barriers to treatment and evaluation. To better assess perceived susceptibility, the revised questionnaire will investigate both what symptoms are “possible to develop” and what symptoms are “likely to develop” as separate questions for both females with Fabry disease and for the patients’ personally. Both patients and healthcare providers should be included in this analysis. Additionally, the creation of a more general questionnaire using data from this analysis may be helpful in the assessment of the health beliefs of females with other X-linked conditions such as ornithine transcarbamylase (OTC) deficiency or hemophilia A or B, providing public health significance to the findings of this study. Future research may demonstrate the utility of these assessments in increasing communication between healthcare providers and their female patients and improving patient outcomes.

APPENDIX A: IRB APPROVAL LETTERS



University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
<http://www.irb.pitt.edu/>

Memorandum

To: Katie Long
From: Sue Beers, Vice Chair
Date: 8/11/2010
IRB#: PRO10060403
Subject: Assessing Health Beliefs among Women Diagnosed and At-Risk for Fabry Disease

The University of Pittsburgh Institutional Review Board reviewed and approved the above referenced study by the expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110. Your research study was approved under:
45 CFR 46.110.(7) characteristics/behaviors

The IRB has approved the waiver for the requirement to obtain a written informed consent.

The IRB has approved the waiver for the requirement to obtain informed consent to use protected health information to identify potential research subjects.

The IRB has approved the advertisement that was submitted for review as written. As a reminder, any changes to the wording of the approved advertisement would require IRB approval prior to distribution.

Approval Date: 8/11/2010
Expiration Date: 8/10/2011

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. The IRB Reference Manual (Chapter 3, Section 3.3) describes the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.



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Institutional Review Board

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Memorandum

To: Katie Long
From: Sue Beers, Vice Chair
Date: 7/8/2011
IRB#: REN11070017 / PRO10060403
Subject: Assessing Health Beliefs among Women Diagnosed and At-Risk for Fabry Disease

Your renewal for the above referenced research study has received expedited review and approval from the Institutional Review Board under:
45 CFR 46.110.(7) characteristics/behaviors

Please note the following information:

Approval Date: 7/8/2011
Expiration Date: 7/7/2012

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. The IRB Reference Manual (Chapter 3, Section 3.3) describes the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least **one month** prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.



University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA
15213
(412) 383-1480
(412) 383-1508
(fax)
<http://www.irb.pitt.edu>

Memorandum

To: Katie Long MS
From: Christopher Ryan PHD, Vice Chair
Date: 6/14/2012
IRB#: REN12050265 / PRO10060403
Subject: Assessing Health Beliefs among Women Diagnosed and At-Risk for Fabry Disease

Your renewal for the above referenced research study has received expedited review and approval from the Institutional Review Board under:
45 CFR 46.110.(7) characteristics/behaviors

Please note the following information:

Approval Date: 6/14/2012
Expiration Date: 6/13/2013

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least **one month** prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center),

FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

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Memorandum

To: Katie Long
From: Christopher Ryan , Vice Chair
Date: 5/22/2013
IRB#: REN13050139 / PRO10060403
Subject: Assessing Health Beliefs among Women Diagnosed and At-Risk for Fabry Disease

Your renewal for the above referenced research study has received expedited review and approval from the Institutional Review Board under:
45 CFR 46.110.(7) characteristics/behaviors

Please note the following information:

Approval Date: 5/22/2013
Expiration Date: 6/13/2014

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least **one month** prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center),

FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

APPENDIX B: PARTICIPANT RECRUITMENT FLYER

Children's Hospital of Pittsburgh
Lysosomal Storage Disorders Program

Research Study For Females At-Risk or Diagnosed with Fabry Disease

Are you interested in helping the Fabry community learn more about the health beliefs of females diagnosed or at-risk for Fabry disease? We are interested in hearing your thoughts and opinions on the diagnosis, management, and treatment of Fabry disease and communication with healthcare professionals.

Eligibility:

- * Female over age 18
- * Known diagnosis of Fabry disease or at-risk based on your family history

Requirements:

- * Complete a 10 minute written survey AND
- * Complete a 15-20 minute open-ended questionnaire

You will receive a \$20 debit card for your participation in this study.



**Please contact principal
investigator Katie Long, MS
CGC if you are interested in
learning more about this
research study.**

**Telephone: 412-692-3475
E-mail: katie.long@chp.edu**

APPENDIX C: TELEPHONE CONSENT SCRIPT

You are being asked to participate in a research study because of your diagnosis of Fabry disease/your family history of Fabry disease and at-risk status. The purpose of this research study is to better understand the health beliefs of women diagnosed and at risk for Fabry disease. To accomplish this, we will be surveying women over age 18 with a diagnosis of Fabry disease or at-risk for the disease based on family history. Participants will be patients with a lysosomal storage disorders program or physician specializing in the care of patients with Fabry disease or have a family member who is a patient of a lysosomal storage disorders program or Fabry specialist.

Women are asked to complete a 5-10 minute written demographics survey including questions about your background (including your age, race, years of education, and family history) and a 15-20 minute written questionnaire about health beliefs. This questionnaire will explore your understanding of and beliefs about Fabry disease and how those factors relate to your health and medical care. When possible, participants are encouraged to complete this questionnaire in the presence of their lysosomal disease healthcare team and to discuss their responses with those professionals. The written demographics survey and questionnaire will not contain your name but will be numbered so your responses can be linked. Additionally, you will be asked to list the names and contact information for your primary Fabry disease healthcare team if you are currently involved in management or treatment for this disease. This information will provide us with the ability to survey your healthcare providers about their health beliefs with regards to the medical management of females with Fabry disease. The survey questions will not ask the healthcare professional for any specific patient information or medical history.

All responses to the survey and questionnaire are confidential and responses will be stored in a secure manner. Personal password-protected computers and a locked file cabinet will be utilized. However, a potential risk of breach of confidentiality remains. Possible exceptions to maintaining confidentiality of your research information include audit of research by the University of Pittsburgh Research Conduct and Compliance Office and subpoena of research data by the courts. Research records for this study will be stored indefinitely. There is a possibility of direct benefit to you as a result of participating in this research study including improved communication with your lysosomal healthcare team about your health beliefs. However, there is no guarantee that you will receive such a benefit. There is also a potential general benefit to increasing the knowledge about women diagnosed or at-risk for Fabry disease. Each participant will receive a \$20 electronic debit card in appreciation for your participation.

Your participation is voluntary and you may withdraw from this project at any time. Your decision to participate or not participate will not impact your current or future relationship with the Lysosomal Storage Disorders Program or its staff, the University of Pittsburgh Medical Center, or the University of Pittsburgh.

You are encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and future questions, concerns or complaints will be answered by a qualified individual or by the Principal Investigator, Katie Long, at 412-692-3475. You may always request that your questions, concerns or complaints be addressed by PI or co-investigator Dr. David Finegold. You may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and

questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable.

APPENDIX D: THANK YOU FLYER

THANK YOU FOR YOUR PARTICIPATION!

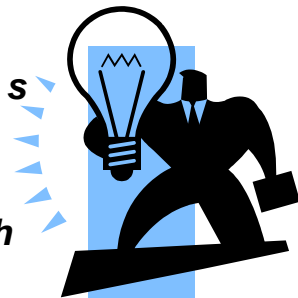
*We truly appreciate your contribution to our
research study.*

Sincerely,

The L ysosomal Storage D isorders P rogram

Staff at the C hildren's

H ospital of P ittsburgh



APPENDIX E: DEMOGRAPHIC SURVEY

Number_____

We thank you for participating in this survey. It is intended to gather demographic information for our study of the health beliefs of females diagnosed and at-risk for Fabry disease. Your answers will be linked by number to your open-ended questionnaire. Please do not write your name on the survey. If there is a question that you do not feel comfortable answering, you can skip it and continue on. Please answer the following questions to the best of your ability. The survey should take approximately 5-10 minutes. Please return the survey by mail in the envelope provided along with your completed open-ended questionnaire. We would like to thank you in advance for your willingness to participate in this study.

1) What is your age?
___ age in years

2) Which one or more of the following would you say is your race? **(Circle all that apply)**

- 1 White
- 2 Black or African American
- 3 Asian
- 4 Native Hawaiian or Other Pacific Islander
- 5 American Indian, Alaska Native
- 6 Other [specify] _____

3) Are you Hispanic or Latino?

- 1 Yes
- 2 No
- 3 Don't know

4) What was the total household income from all sources last year?

- 1 Less than \$10,000
- 2 Between \$10,000 and \$20,000
- 3 Between \$20,001 and \$35,000
- 4 Between \$35,001 and \$50,000
- 5 Between \$50,001 and \$75,000
- 6 Greater than \$75,000

5) What is the highest grade or year of school you completed?

- 1 Grades 8 or less (Elementary)
- 2 Grades 9 through 11 (Some high school)
- 3 Grade 12 or GED (High school graduate)
- 4 College 1 year to 3 years (Some college or technical school)
- 5 College 4 years or more (College graduate or post-graduate)
- 6 Graduate level (Masters or PhD)

6) Are you currently employed (includes part and full time)?

- 1 Yes
- 2 No

Number_____

7) What is your marital status?

- 1 Single
- 2 Married
- 3 Divorced
- 4 Separated
- 5 Widowed

8) Do you have any kind of health care coverage, including health insurance, prepaid plans such as HMOs, or government plans such as Medicare/Medicaid?

- 1 Yes
- 2 No
- 3 Don't know / Not sure

9) Was there a time in the past 12 months when you needed to see a doctor but could not because of the cost?

- 1 Yes
- 2 No
- 3 Don't know / Not sure

10) Do you have a diagnosis of Fabry disease?

- 1 Yes
- 2 No
- 3 Don't know / Not sure

10a) If you answered "No" or "Don't know" to the previous question, are you at risk to have inherited Fabry disease based on your family history?

- 1 Yes
- 2 No
- 3 Don't know / Not sure

11) Do you have a family history of Fabry disease in any relative?

- 1 Yes
- 2 No
- 3 Don't know / Not sure

11a) If you answered "Yes" to the previous question, please select all of your relatives who have ever been diagnosed with Fabry disease.

- | | | |
|-----------------------------------|---|---|
| <input type="checkbox"/> Mother | <input type="checkbox"/> Maternal Grandfather | <input type="checkbox"/> Paternal Grandfather |
| <input type="checkbox"/> Father | <input type="checkbox"/> Maternal Grandmother | <input type="checkbox"/> Paternal Grandmother |
| <input type="checkbox"/> Brother | <input type="checkbox"/> Maternal Aunt | <input type="checkbox"/> Paternal Aunt |
| <input type="checkbox"/> Sister | <input type="checkbox"/> Maternal Uncle | <input type="checkbox"/> Paternal Uncle |
| <input type="checkbox"/> Son | <input type="checkbox"/> Maternal Cousin | <input type="checkbox"/> Paternal Cousin |
| <input type="checkbox"/> Daughter | <input type="checkbox"/> Niece | <input type="checkbox"/> Nephew |

Number_____

11b) If you answered “Yes” to question 11, have any of your relatives received treatment for Fabry disease with enzyme replacement therapy?

1 Yes

2 No

3 Don't know / Not sure

APPENDIX F: CLINICAL QUESTIONNAIRE

Assessing Health Beliefs of Women Diagnosed and At Risk for Fabry Disease

Thank you for agreeing to complete this questionnaire. Please complete each question as instructed.

Symptoms of Fabry Disease

1. Based on your understanding, what symptoms can Fabry disease cause? (Mark all that apply)

| | |
|---|---|
| In males: | |
| <input type="checkbox"/> Proteinuria (excess protein in the urine) | <input type="checkbox"/> Kidney failure |
| <input type="checkbox"/> Congestive heart failure (heart cannot pump enough blood to meet the body's needs) | <input type="checkbox"/> Heart attack |
| <input type="checkbox"/> Enlargement of heart | <input type="checkbox"/> Abnormal heart rhythm (irregular heart beat) |
| <input type="checkbox"/> Stroke | <input type="checkbox"/> Transient ischemic attack (mini-stroke) |
| <input type="checkbox"/> Chronic pain | <input type="checkbox"/> Burning/numbness/tingling in hands or feet |
| <input type="checkbox"/> Heat and/or cold intolerance | <input type="checkbox"/> Problems with sweating |
| <input type="checkbox"/> Abdominal pain | <input type="checkbox"/> Diarrhea and/or constipation |
| <input type="checkbox"/> Angiokeratomas (clustered red skin markings) | <input type="checkbox"/> Corneal whorls (pattern on transparent area of eye only visible by slit lamp exam) |
| <input type="checkbox"/> Pulmonary (lung) disease | <input type="checkbox"/> Depression and/or anxiety |

| | |
|---|---|
| In females: | |
| <input type="checkbox"/> Proteinuria (excess protein in the urine) | <input type="checkbox"/> Kidney failure |
| <input type="checkbox"/> Congestive heart failure (heart cannot pump enough blood to meet the body's needs) | <input type="checkbox"/> Heart attack |
| <input type="checkbox"/> Enlargement of heart | <input type="checkbox"/> Abnormal heart rhythm (irregular heart beat) |
| <input type="checkbox"/> Stroke | <input type="checkbox"/> Transient ischemic attack (mini-stroke) |
| <input type="checkbox"/> Chronic pain | <input type="checkbox"/> Burning/numbness/tingling in hands or feet |
| <input type="checkbox"/> Heat and/or cold intolerance | <input type="checkbox"/> Problems with sweating |
| <input type="checkbox"/> Abdominal pain | <input type="checkbox"/> Diarrhea and/or constipation |
| <input type="checkbox"/> Angiokeratomas (clustered red skin markings) | <input type="checkbox"/> Corneal whorls (pattern on transparent area of eye only visible by slit lamp exam) |
| <input type="checkbox"/> Pulmonary (lung) disease | <input type="checkbox"/> Depression and/or anxiety |

2. What symptoms of Fabry disease, if any, do you have? (Mark all that apply)

| | |
|---|---|
| <input type="checkbox"/> Proteinuria (excess protein in the urine) | <input type="checkbox"/> Kidney failure |
| <input type="checkbox"/> Congestive heart failure (heart cannot pump enough blood to meet the body's needs) | <input type="checkbox"/> Heart attack |
| <input type="checkbox"/> Enlargement of heart | <input type="checkbox"/> Abnormal heart rhythm (irregular heart beat) |
| <input type="checkbox"/> Stroke | <input type="checkbox"/> Transient ischemic attack (mini-stroke) |
| <input type="checkbox"/> Chronic pain | <input type="checkbox"/> Burning/numbness/tingling in hands or feet |
| <input type="checkbox"/> Heat and/or cold intolerance | <input type="checkbox"/> Problems with sweating |
| <input type="checkbox"/> Abdominal pain | <input type="checkbox"/> Diarrhea and/or constipation |
| <input type="checkbox"/> Angiokeratomas (clustered red skin markings) | <input type="checkbox"/> Corneal whorls (pattern on transparent area of eye only visible by slit lamp exam) |
| <input type="checkbox"/> Pulmonary (lung) disease | <input type="checkbox"/> Depression and/or anxiety |

3. What symptoms of Fabry disease, if any, do you feel you are likely to develop? (Mark all that apply)

| | |
|---|---|
| <input type="checkbox"/> Proteinuria (excess protein in the urine) | <input type="checkbox"/> Kidney failure |
| <input type="checkbox"/> Congestive heart failure (heart cannot pump enough blood to meet the body's needs) | <input type="checkbox"/> Heart attack |
| <input type="checkbox"/> Enlargement of heart | <input type="checkbox"/> Abnormal heart rhythm (irregular heart beat) |
| <input type="checkbox"/> Stroke | <input type="checkbox"/> Transient ischemic attack (mini-stroke) |
| <input type="checkbox"/> Chronic pain | <input type="checkbox"/> Burning/numbness/tingling in hands or feet |
| <input type="checkbox"/> Heat and/or cold intolerance | <input type="checkbox"/> Problems with sweating |
| <input type="checkbox"/> Abdominal pain | <input type="checkbox"/> Diarrhea and/or constipation |
| <input type="checkbox"/> Angiokeratomas (clustered red skin markings) | <input type="checkbox"/> Corneal whorls (pattern on transparent area of eye only visible by slit lamp exam) |
| <input type="checkbox"/> Pulmonary (lung) disease | <input type="checkbox"/> Depression and/or anxiety |

Seriousness of Fabry Disease

4. How serious is Fabry disease?

a. For a male: (circle one)

- i. Fabry disease is very serious.
- ii. Fabry disease is somewhat serious.
- iii. Fabry disease can be serious, but is not always serious.
- iv. Fabry disease is not serious.

b. For a female: (circle one)

- i. Fabry disease is very serious.
- ii. Fabry disease is somewhat serious.
- iii. Fabry disease can be serious, but is not always serious.
- iv. Fabry disease is not serious.

5. What statement would you most agree with? (circle one)
- i. I am very worried about Fabry disease.
 - ii. I am somewhat worried about Fabry disease.
 - iii. I am worried very little about Fabry disease.
 - iv. I am not worried about Fabry disease.
- a. If you are worried about Fabry disease, what worries you the most? Please describe.

Inheritance of Fabry Disease

6. Based on your understanding, how is Fabry disease passed on in a family?

7. Have you ever used the word carrier to describe yourself?

| | |
|------------------------------|-----------------------------|
| <input type="checkbox"/> Yes | <input type="checkbox"/> No |
|------------------------------|-----------------------------|

- a. Have any of your physicians or health care providers used the word “carrier” to describe your diagnosis?

| | |
|------------------------------|-----------------------------|
| <input type="checkbox"/> Yes | <input type="checkbox"/> No |
|------------------------------|-----------------------------|

- b. Do you think this term is appropriate?

| | |
|------------------------------|-----------------------------|
| <input type="checkbox"/> Yes | <input type="checkbox"/> No |
|------------------------------|-----------------------------|

- i. Why or why not?

Diagnosis of Fabry Disease

8. Have you ever been diagnosed* with Fabry disease?

**A diagnosis can be made by genetic testing or by family history alone.*

| | | |
|------------------------------|-----------------------------|---------------------------------|
| <input type="checkbox"/> Yes | <input type="checkbox"/> No | <input type="checkbox"/> Unsure |
|------------------------------|-----------------------------|---------------------------------|

If answered no or unsure, please continue to question 8 part f (page 5).

If answered yes, please answer the following:

a. Which of these scenarios most accurately describes the situation that led to your diagnosis? (Mark all that apply)

| |
|---|
| <input type="checkbox"/> A family member was diagnosed with Fabry disease |
| <input type="checkbox"/> My own symptoms |
| <input type="checkbox"/> Other: _____ |

b. Which center/clinic manages your diagnosis of Fabry disease?

| | |
|---|--|
| <input type="checkbox"/> Emory Genetics | <input type="checkbox"/> Weisskopf Child Evaluation Center |
| <input type="checkbox"/> Massachusetts General Hospital | <input type="checkbox"/> Cincinnati Children's Hospital |
| <input type="checkbox"/> University of Washington | <input type="checkbox"/> Children's Hospital of Wisconsin |
| <input type="checkbox"/> Children's Hospital of Chicago | <input type="checkbox"/> University of Colorado Hospital |
| <input type="checkbox"/> Other: _____ | |

c. Before you were diagnosed did you have any signs or symptoms of Fabry disease?

| | |
|------------------------------|-----------------------------|
| <input type="checkbox"/> Yes | <input type="checkbox"/> No |
|------------------------------|-----------------------------|

i. If yes, mark all of the signs or symptoms that apply.

| | |
|---|---|
| <input type="checkbox"/> Proteinuria (excess protein in the urine) | <input type="checkbox"/> Kidney failure |
| <input type="checkbox"/> Congestive heart failure (heart cannot pump enough blood to meet the body's needs) | <input type="checkbox"/> Heart attack |
| <input type="checkbox"/> Enlargement of heart | <input type="checkbox"/> Abnormal heart rhythm (irregular heart beat) |
| <input type="checkbox"/> Stroke | <input type="checkbox"/> Transient ischemic attack (mini-stroke) |
| <input type="checkbox"/> Chronic pain | <input type="checkbox"/> Burning/numbness/tingling in hands or feet |
| <input type="checkbox"/> Heat and/or cold intolerance | <input type="checkbox"/> Problems with sweating |
| <input type="checkbox"/> Abdominal pain | <input type="checkbox"/> Diarrhea and/or constipation |
| <input type="checkbox"/> Angiokeratomas (clustered red skin markings) | <input type="checkbox"/> Corneal whorls (pattern on transparent area of eye only visible by slit lamp exam) |
| <input type="checkbox"/> Pulmonary (lung) disease | <input type="checkbox"/> Depression and/or anxiety |

d. How did you feel about receiving a diagnosis of Fabry disease? Please describe.

e. Did your diagnosis of Fabry disease impact your ideas about your health?

| | |
|------------------------------|-----------------------------|
| <input type="checkbox"/> Yes | <input type="checkbox"/> No |
|------------------------------|-----------------------------|

i. If yes, please describe how it impacted your ideas about your health.

If answered no or unsure to question 8, please answer the following:

f. Have you been tested for Fabry disease?

| | |
|------------------------------|-----------------------------|
| <input type="checkbox"/> Yes | <input type="checkbox"/> No |
|------------------------------|-----------------------------|

g. If you have not been tested, what are your reasons for not seeking testing?

Clinical Care and Monitoring of Fabry Disease

9. In the care of your Fabry disease, which of these evaluations, if any, have been recommended to you? (Mark all that apply)

| | |
|---|--|
| <input type="checkbox"/> 24 hour urine test (test for kidney function) | <input type="checkbox"/> Renal (kidney) biopsy |
| <input type="checkbox"/> Electrocardiogram/EKG (records heart's electrical activity using electrodes) | <input type="checkbox"/> Echocardiogram (ultrasound of the heart) |
| <input type="checkbox"/> 24 hour holter heart monitoring (cardiac event monitoring) | <input type="checkbox"/> Heart MRI (uses magnets to create a picture of the heart) |
| <input type="checkbox"/> Audiologic (hearing) evaluation | <input type="checkbox"/> Pulmonary (lung) function test (breathing test) |
| <input type="checkbox"/> Brain MRI (uses magnets to create a picture of the brain) | <input type="checkbox"/> Slit Lamp eye exam |
| <input type="checkbox"/> Fabrazyme antibody testing (blood test) | <input type="checkbox"/> GL-3 testing (blood or urine test) |
| <input type="checkbox"/> Lipid panel (cholesterol blood test) | |

- a. Of the following evaluations recommended to you, which did you complete at the time of your diagnosis? (Mark all that apply)

| | |
|---|--|
| <input type="checkbox"/> 24 hour urine test (test for kidney function) | <input type="checkbox"/> Renal (kidney) biopsy |
| <input type="checkbox"/> Electrocardiogram/EKG (records heart's electrical activity using electrodes) | <input type="checkbox"/> Echocardiogram (ultrasound of the heart) |
| <input type="checkbox"/> 24 hour holter heart monitoring (cardiac event monitoring) | <input type="checkbox"/> Heart MRI (uses magnets to create a picture of the heart) |
| <input type="checkbox"/> Audiologic (hearing) evaluation | <input type="checkbox"/> Pulmonary (lung) function test (breathing test) |
| <input type="checkbox"/> Brain MRI (uses magnets to create a picture of the brain) | <input type="checkbox"/> Slit Lamp eye exam |
| <input type="checkbox"/> Fabrazyme antibody testing (blood test) | <input type="checkbox"/> GL-3 testing (blood or urine test) |
| <input type="checkbox"/> Lipid panel (cholesterol blood test) | |

- b. Of the following evaluations recommended to you, which do you continue to follow on a regular basis? (Mark all that apply)

| | |
|---|--|
| <input type="checkbox"/> 24 hour urine test (test for kidney function) | <input type="checkbox"/> Renal (kidney) biopsy |
| <input type="checkbox"/> Electrocardiogram/EKG (records heart's electrical activity using electrodes) | <input type="checkbox"/> Echocardiogram (ultrasound of the heart) |
| <input type="checkbox"/> 24 hour holter heart monitoring (cardiac event monitoring) | <input type="checkbox"/> Heart MRI (uses magnets to create a picture of the heart) |
| <input type="checkbox"/> Audiologic (hearing) evaluation | <input type="checkbox"/> Pulmonary (lung) function test (breathing test) |
| <input type="checkbox"/> Brain MRI (uses magnets to create a picture of the brain) | <input type="checkbox"/> Slit Lamp eye exam |
| <input type="checkbox"/> Fabrazyme antibody testing (blood test) | <input type="checkbox"/> GL-3 testing (blood or urine test) |
| <input type="checkbox"/> Lipid panel (cholesterol blood test) | |

10. Do any of the following prevent you from participating in recommended evaluations and monitoring? (Mark all that apply)

| | |
|--|--|
| <input type="checkbox"/> Time | <input type="checkbox"/> Distance from centers |
| <input type="checkbox"/> Difficulties obtaining transportation | <input type="checkbox"/> Costs not covered by insurance |
| <input type="checkbox"/> Lack of insurance | <input type="checkbox"/> Insurance or work discrimination |
| <input type="checkbox"/> Job Responsibilities | <input type="checkbox"/> Symptoms are not severe |
| <input type="checkbox"/> Childcare responsibilities | <input type="checkbox"/> Care of family member affected with Fabry |
| <input type="checkbox"/> Not enough information about assessments | <input type="checkbox"/> Frustration with the amount of recommended tests |
| <input type="checkbox"/> Poor Health | <input type="checkbox"/> Lack of support or encouragement |
| <input type="checkbox"/> Frustration with lack of provider knowledge about Fabry disease | <input type="checkbox"/> Concern about test results/finding a health problem |
| <input type="checkbox"/> Fear of testing procedure(s) | <input type="checkbox"/> Worry |
| <input type="checkbox"/> Sadness | <input type="checkbox"/> Feeling overwhelmed |
| <input type="checkbox"/> Desire to keep focus on more severely affected family member(s) | <input type="checkbox"/> Guilt |
| <input type="checkbox"/> Feeling undeserving of care or attention | <input type="checkbox"/> Anger about diagnosis |
| <input type="checkbox"/> Depression/excessive sadness | <input type="checkbox"/> Anxiety/excessive worry |

- a. Please elaborate on any of the factors you marked above OR if there are any factors not listed above that impact your participation in recommended evaluations and monitoring please describe them here.

11. Are you currently receiving enzyme replacement therapy (ERT)?

| | |
|------------------------------|-----------------------------|
| <input type="checkbox"/> Yes | <input type="checkbox"/> No |
|------------------------------|-----------------------------|

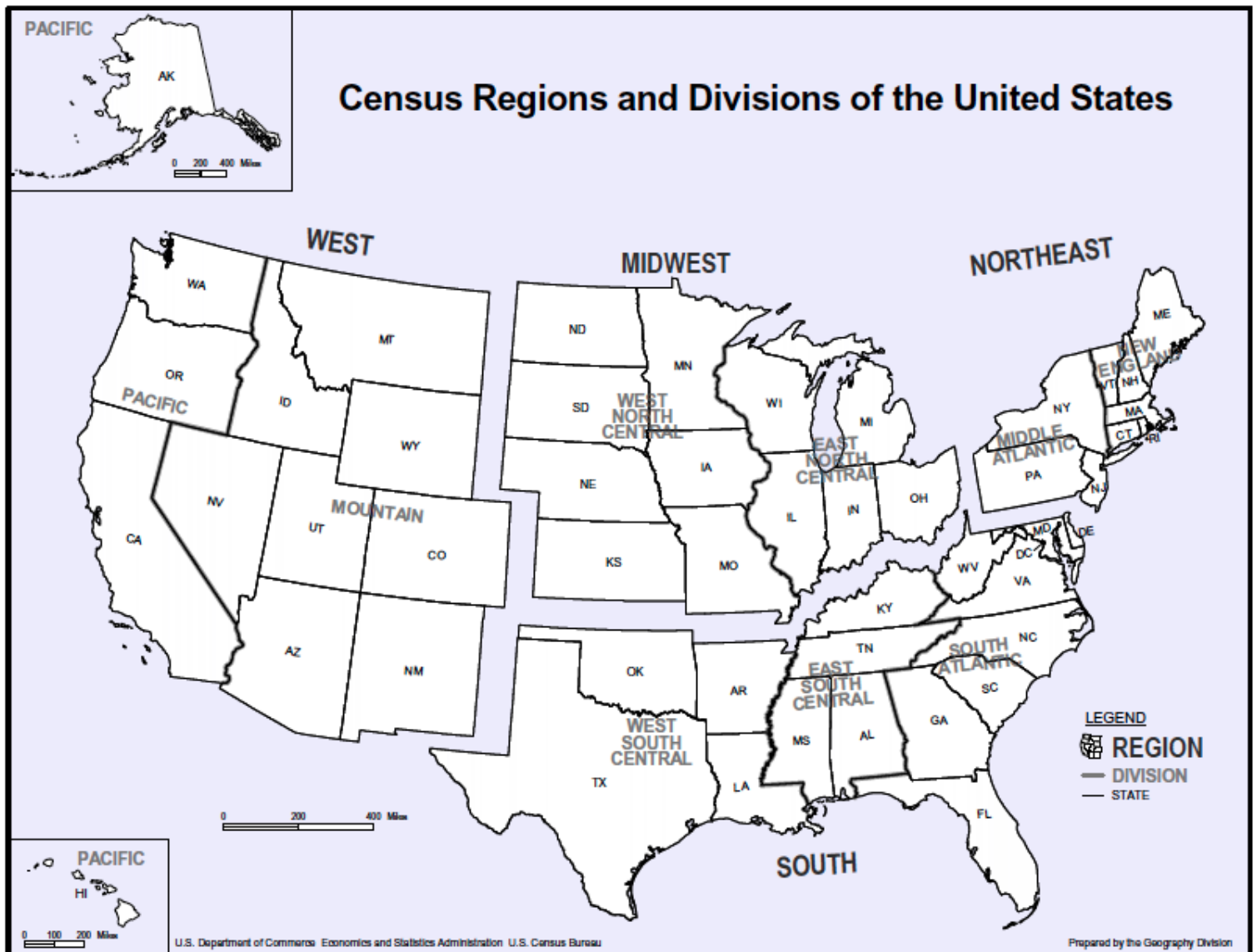
If answered yes, please answer the following:

- a. What were your expectations for how ERT could improve your health?
- b. Please describe how ERT did or did not meet your expectations?

12. Please list any other issues or concerns regarding your Fabry disease not discussed in this questionnaire.

We value your input. Thank you for completing this questionnaire.

APPENDIX G: CENSUS REGIONS AND DIVISIONS OF THE UNITED STATES



BIBLIOGRAPHY

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2. MacDermot, K.D., Holmes, A., and Miners, A.H. (2001). Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. *Journal of medical genetics* 38, 769-775.
3. MacDermot, K.D., Holmes, A., and Miners, A.H. (2001). Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. *Journal of medical genetics* 38, 750-760.
4. Eng, C.M., Germain, D.P., Banikazemi, M., Warnock, D.G., Wanner, C., Hopkin, R.J., Bultas, J., Lee, P., Sims, K., Brodie, S.E., et al. (2006). Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. *Genetics in medicine : official journal of the American College of Medical Genetics* 8, 539-548.
5. Wang, R.Y., Lelis, A., Mirocha, J., and Wilcox, W.R. (2007). Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. *Genetics in medicine : official journal of the American College of Medical Genetics* 9, 34-45.
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